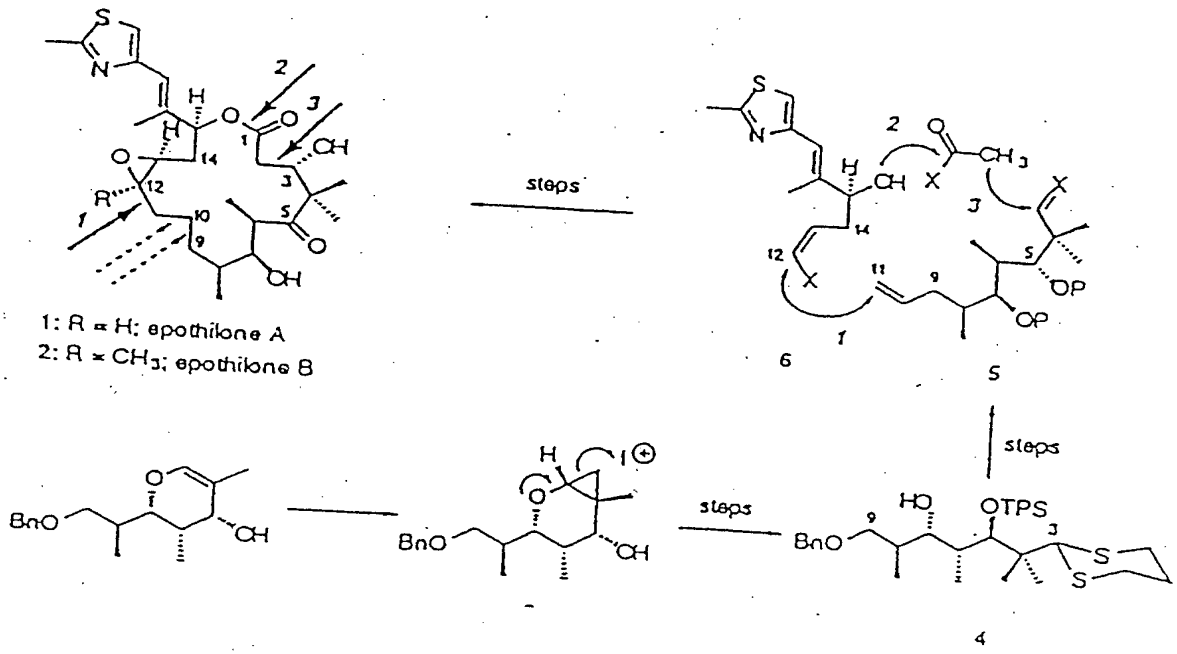
(A)


steps
1: R = H; epothilone A
2: R = CH3; epothilone B
6
5
steps
steps
4

(B)

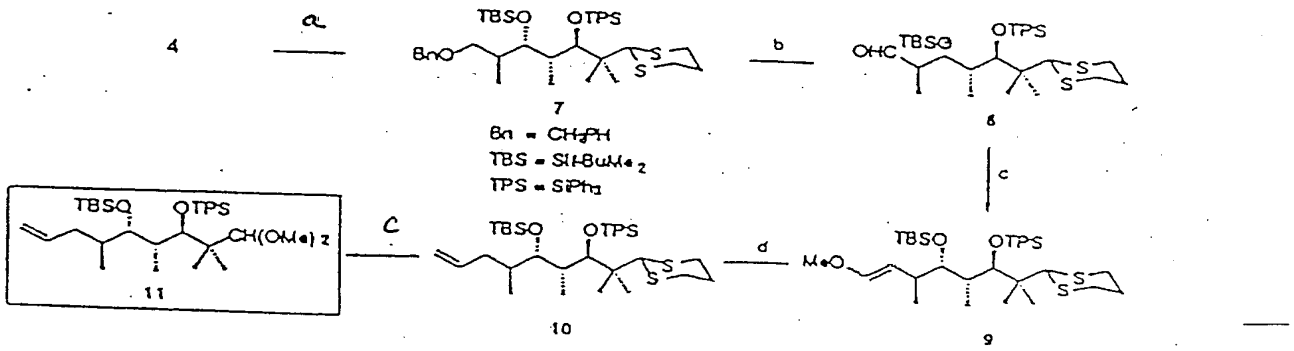

4
a
b
c
d
7
8
9
10
11
Bn = CH2Ph
TBS = SiMe2t-Bu
TPS = SiPh3

Figure 1

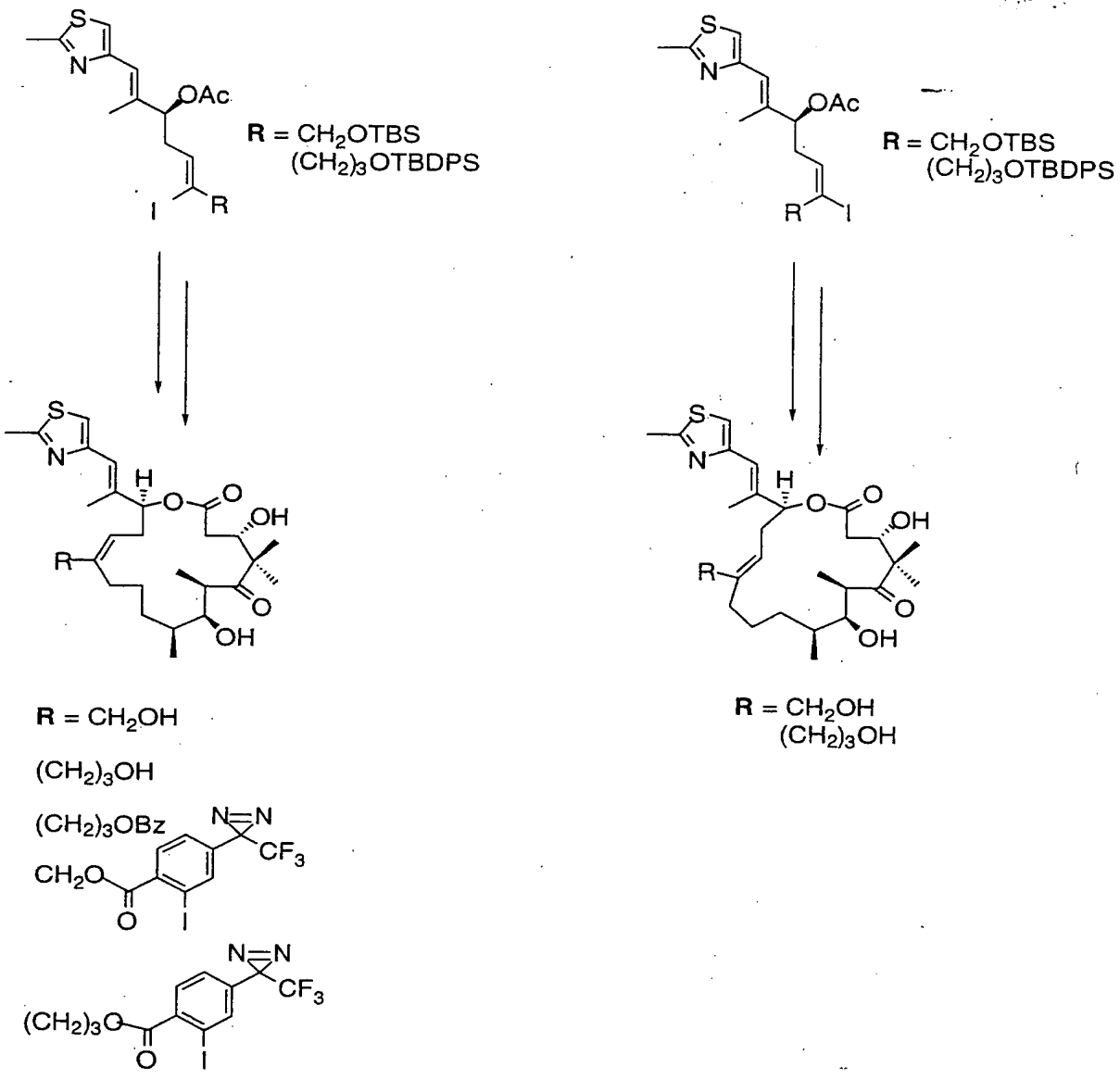


Figure 2

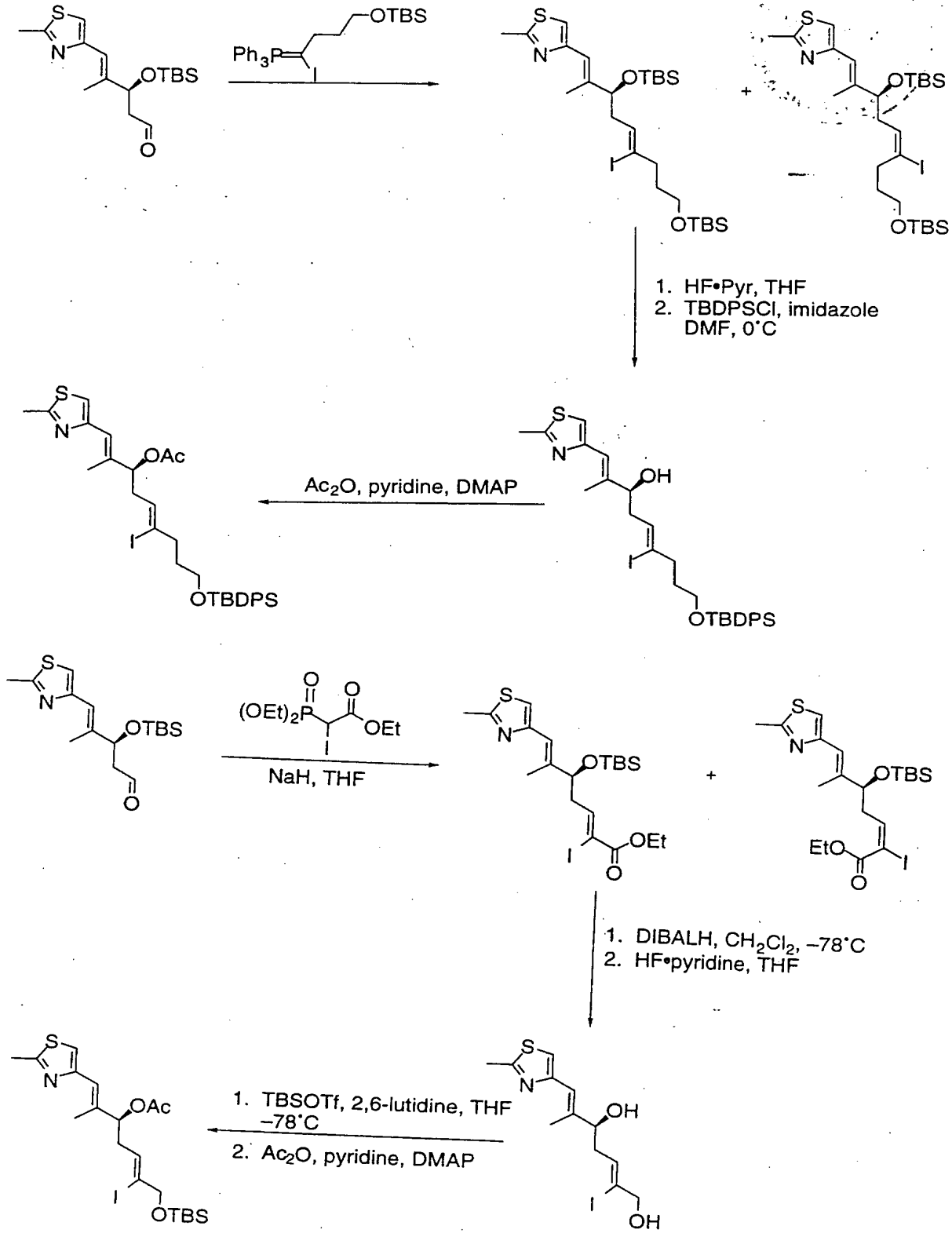

OTBS
Ph3P
I
OTBS
OTBS
OTBS
OTBS
1. HF•Pyr, THF
2. TBDPSCl, imidazole
DMF, 0°C
OAc
Ac2O, pyridine, DMAP
OH
OTBDPS
OTBDPS
OTBS
(OEt)2P
O
OEt
I
NaH, THF
OTBS
OEt
OTBS
EtO
1. DIBALH, CH2Cl2, –78°C
2. HF•pyridine, THF
OAc
1. TBSOTf, 2,6-lutidine, THF
–78°C
2. Ac2O, pyridine, DMAP
OH
OTBS
OH

Figure 3(A)

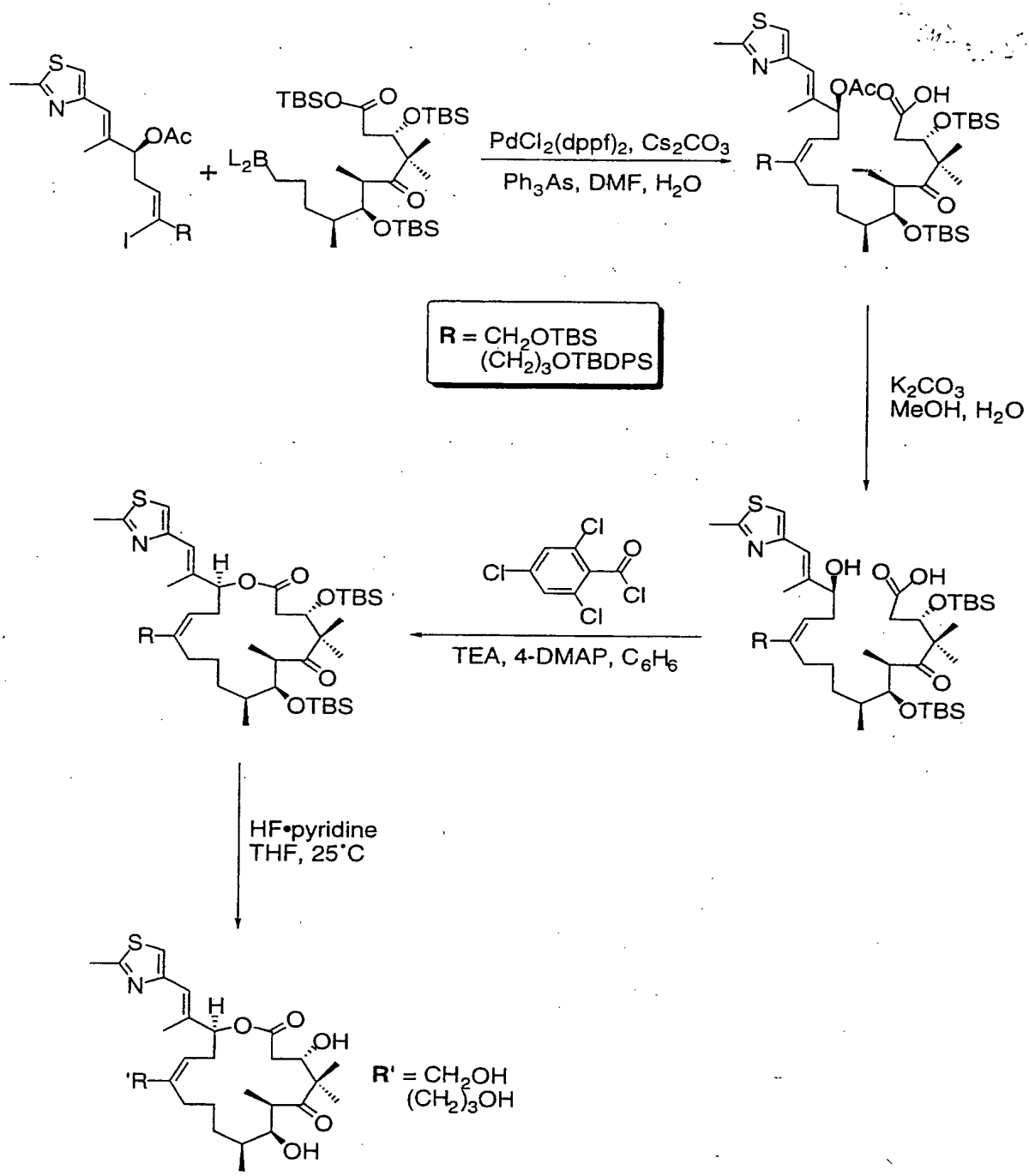
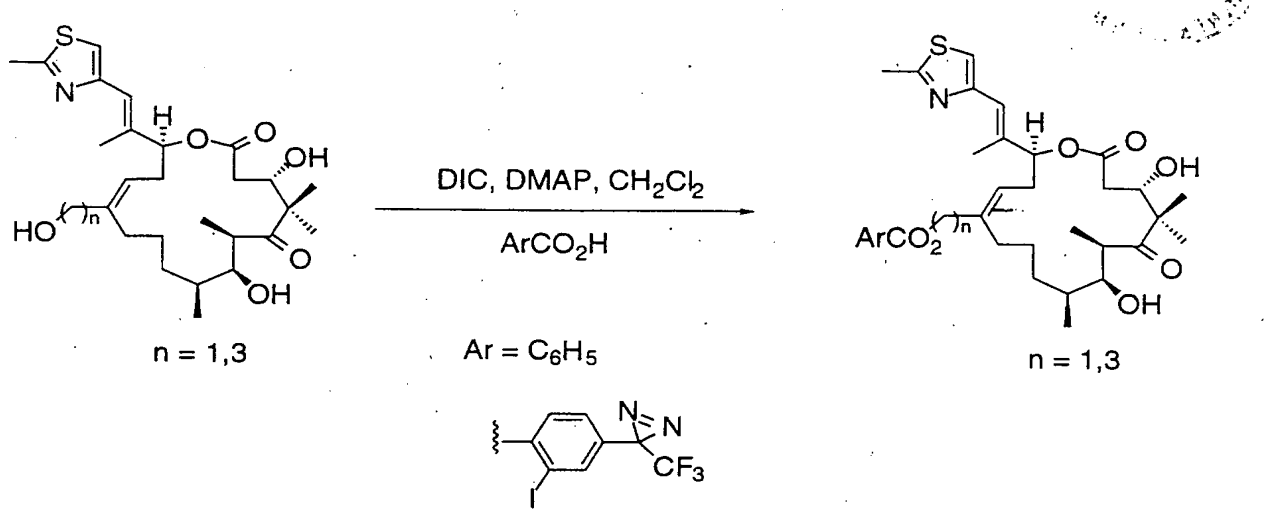


Fig. 3(B)



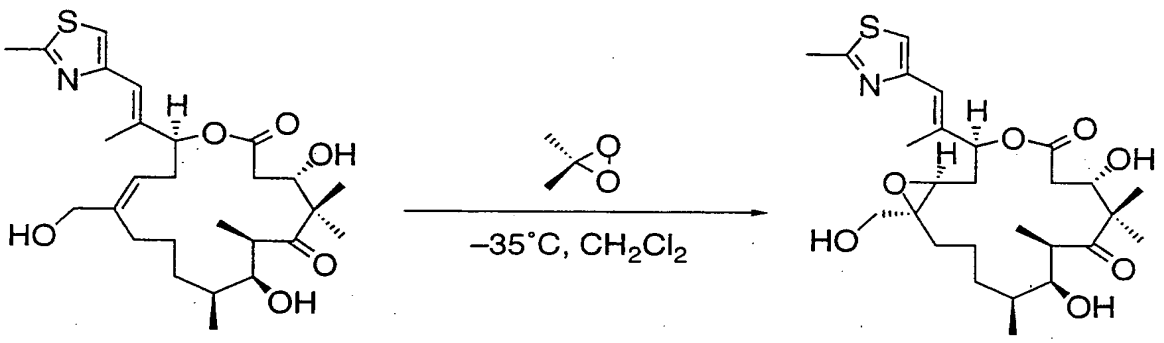


Fig. 3(C)

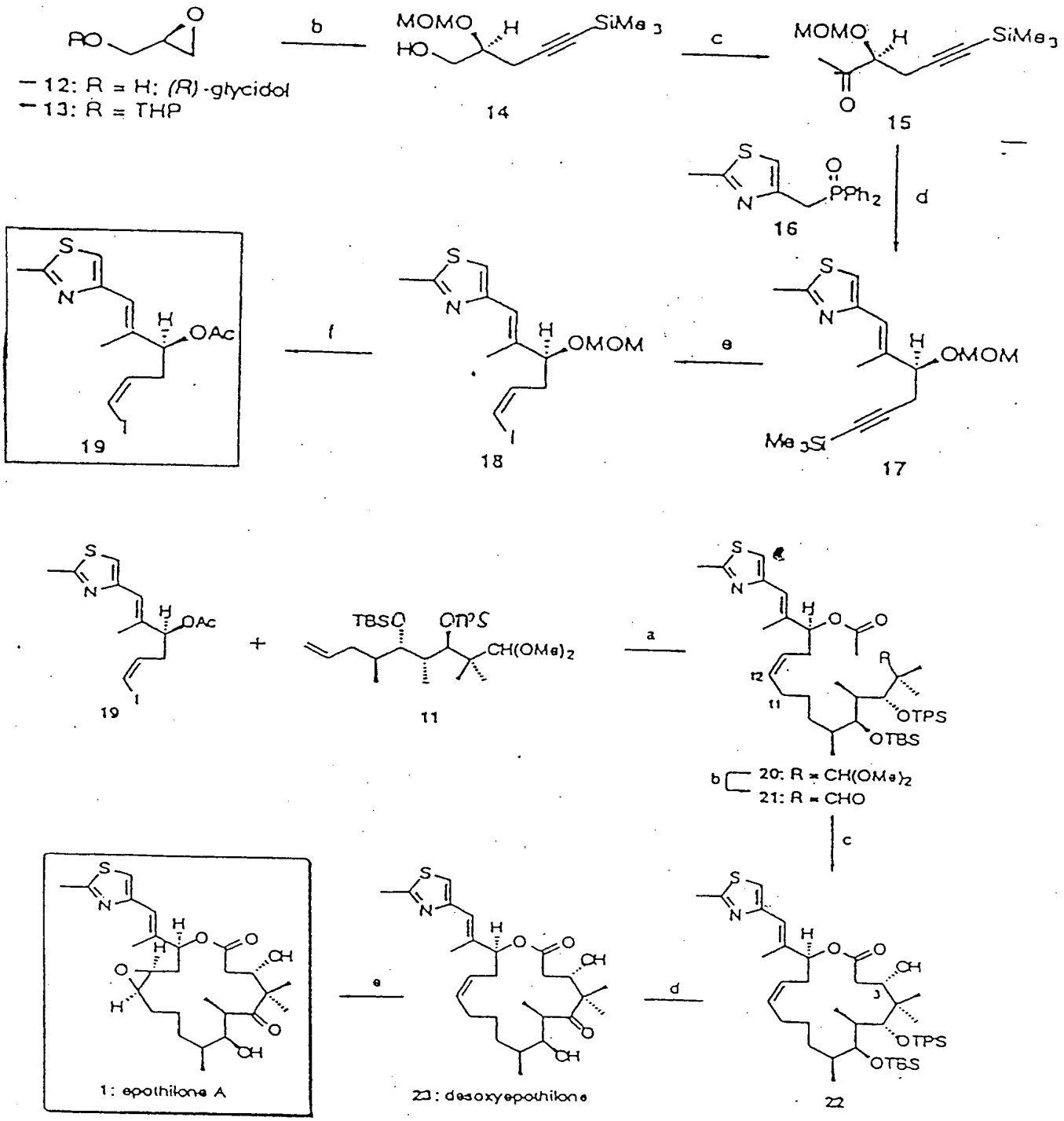

12: R = H; (R)-glycidol
13: R = THP
14
15
16
17
18
19
20: R = CH(OMe)2
21: R = CHO
22
23: desoxyepothilone
1: epothilone A
TBSO
OTPS
CH(OMe)2
OTBS
OMOM
OAc
SiMe3
Me3Si
PPh2

Figure 4

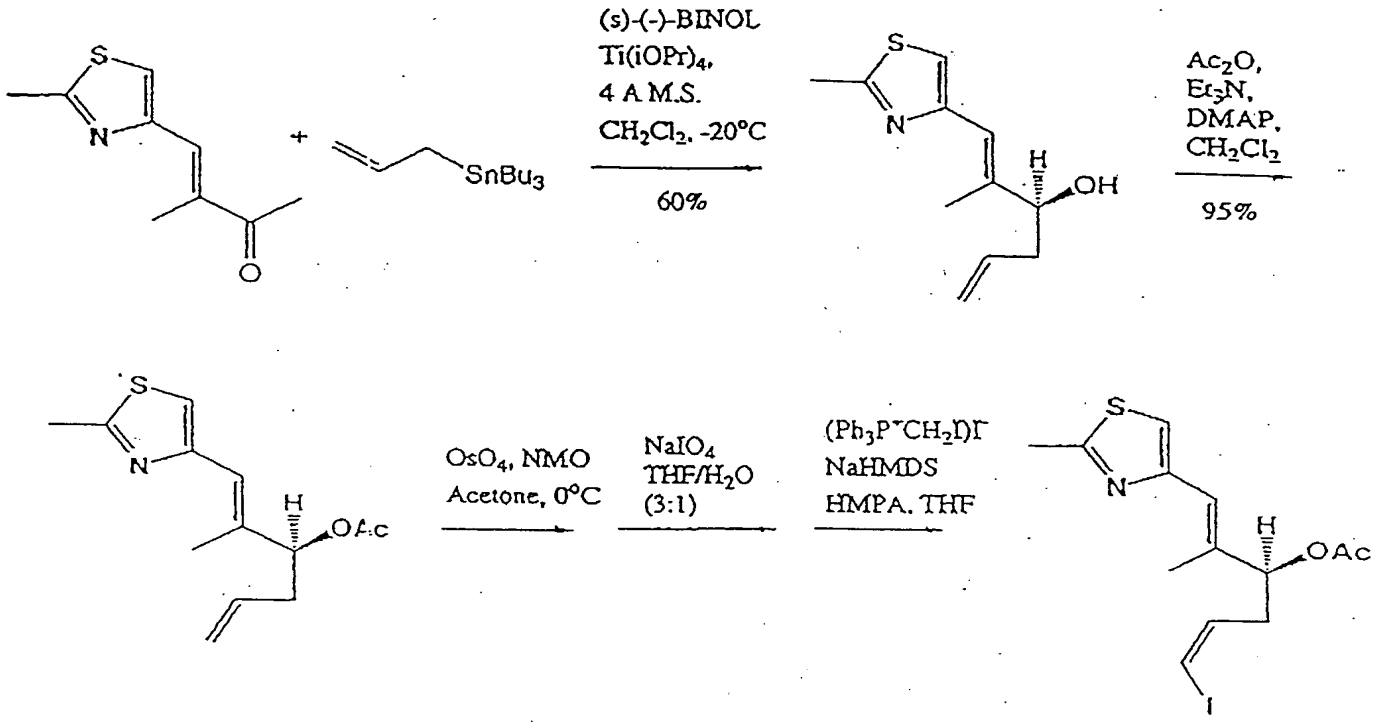
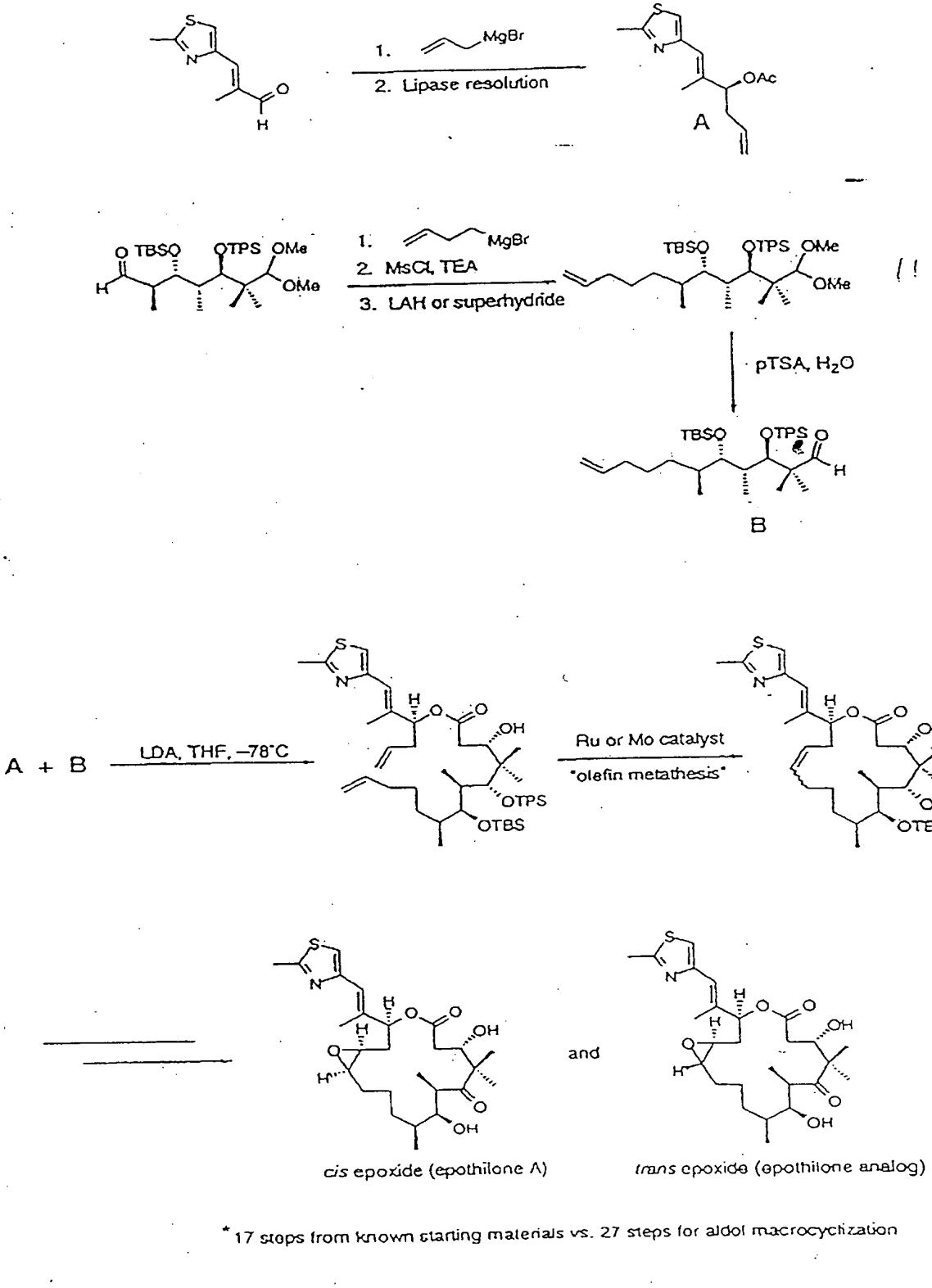
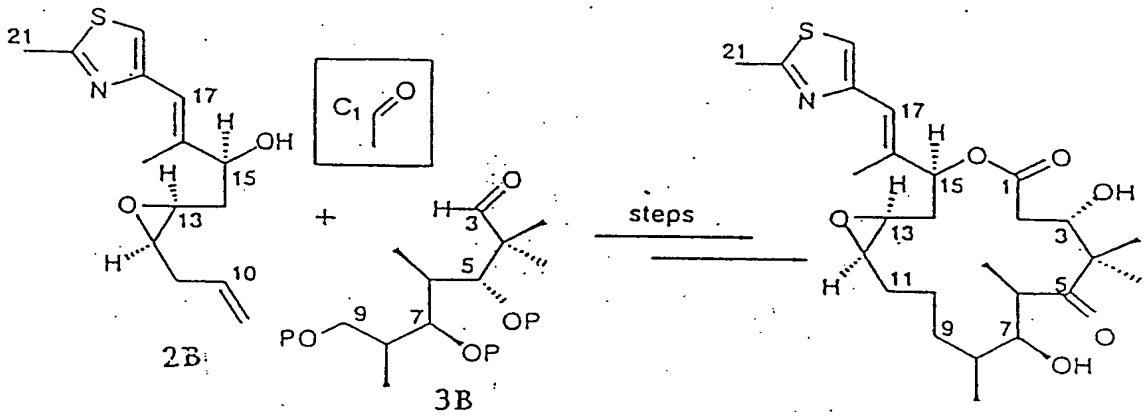


Figure 5



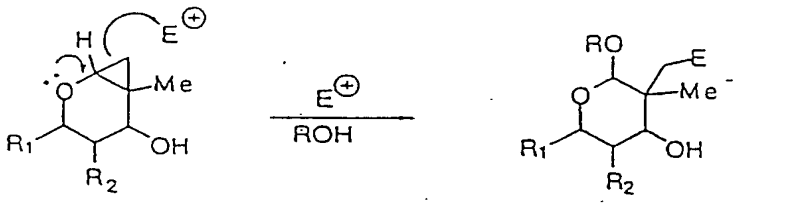
*17 steps from known starting materials vs. 27 steps for aldol macrocyclization

Figure 6



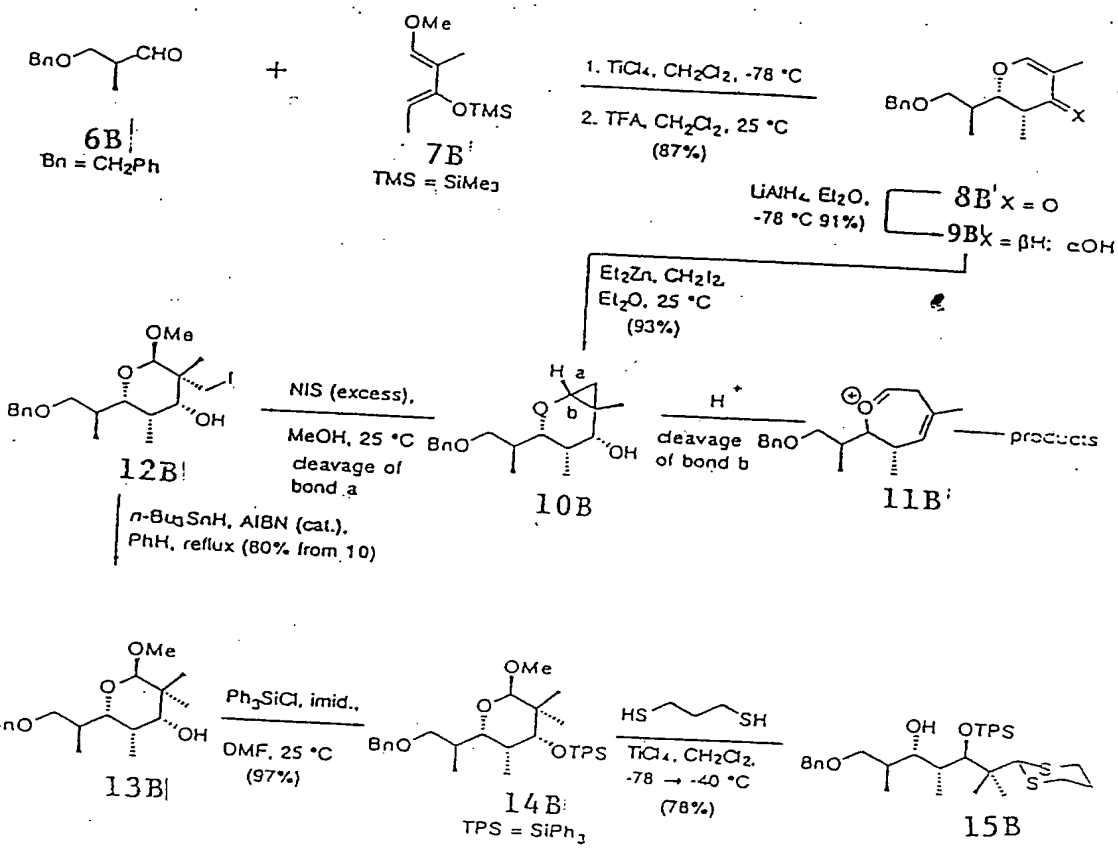
P = unspecified protecting group 1 : epothilone A

Convergent strategy for a total synthesis of epothilone A (1).



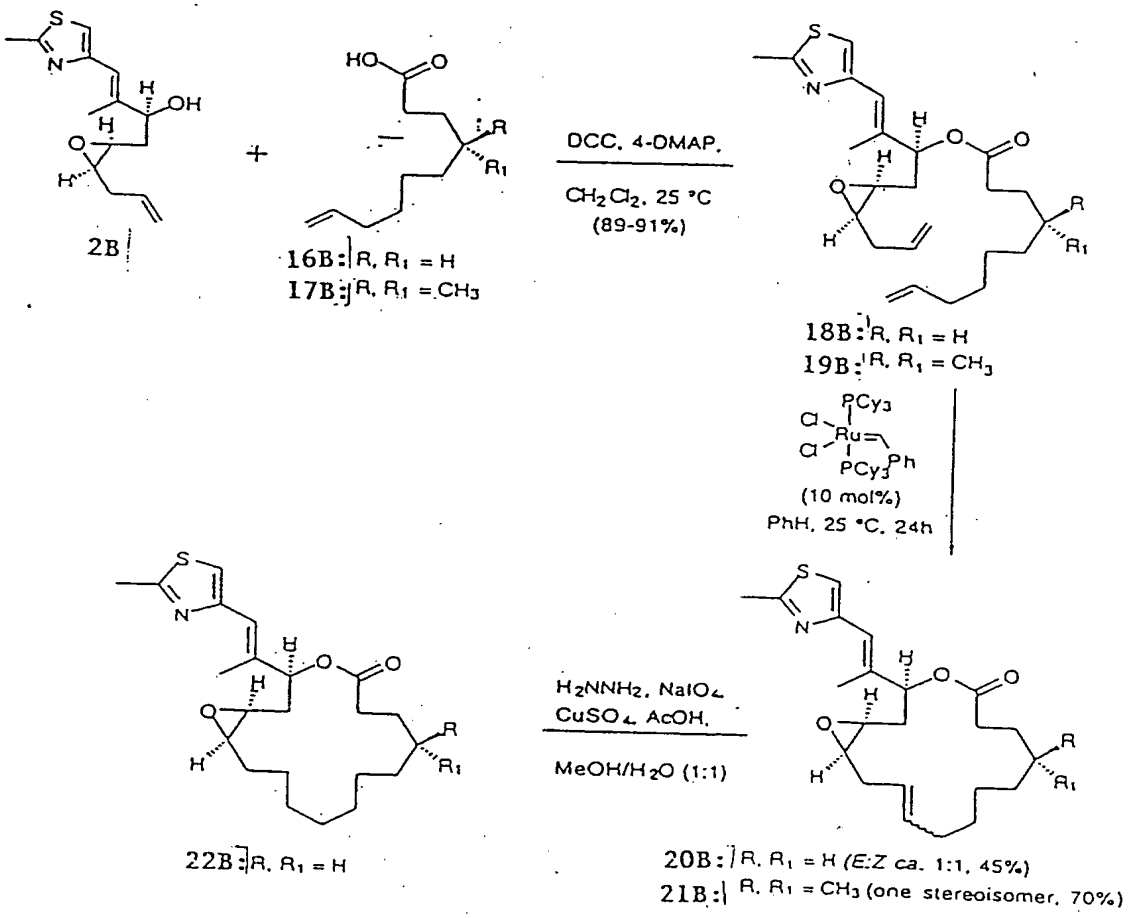
The glycal cyclopropane solvolysis strategy for the introduction of geminal methyl groups.

Figure 7



Enantioselective synthesis of compound 15B

Figure 8



Construction of epothilone model systems 20^B, 21^B, and 22^B by ring-closing olefin metathesis

Figure 9

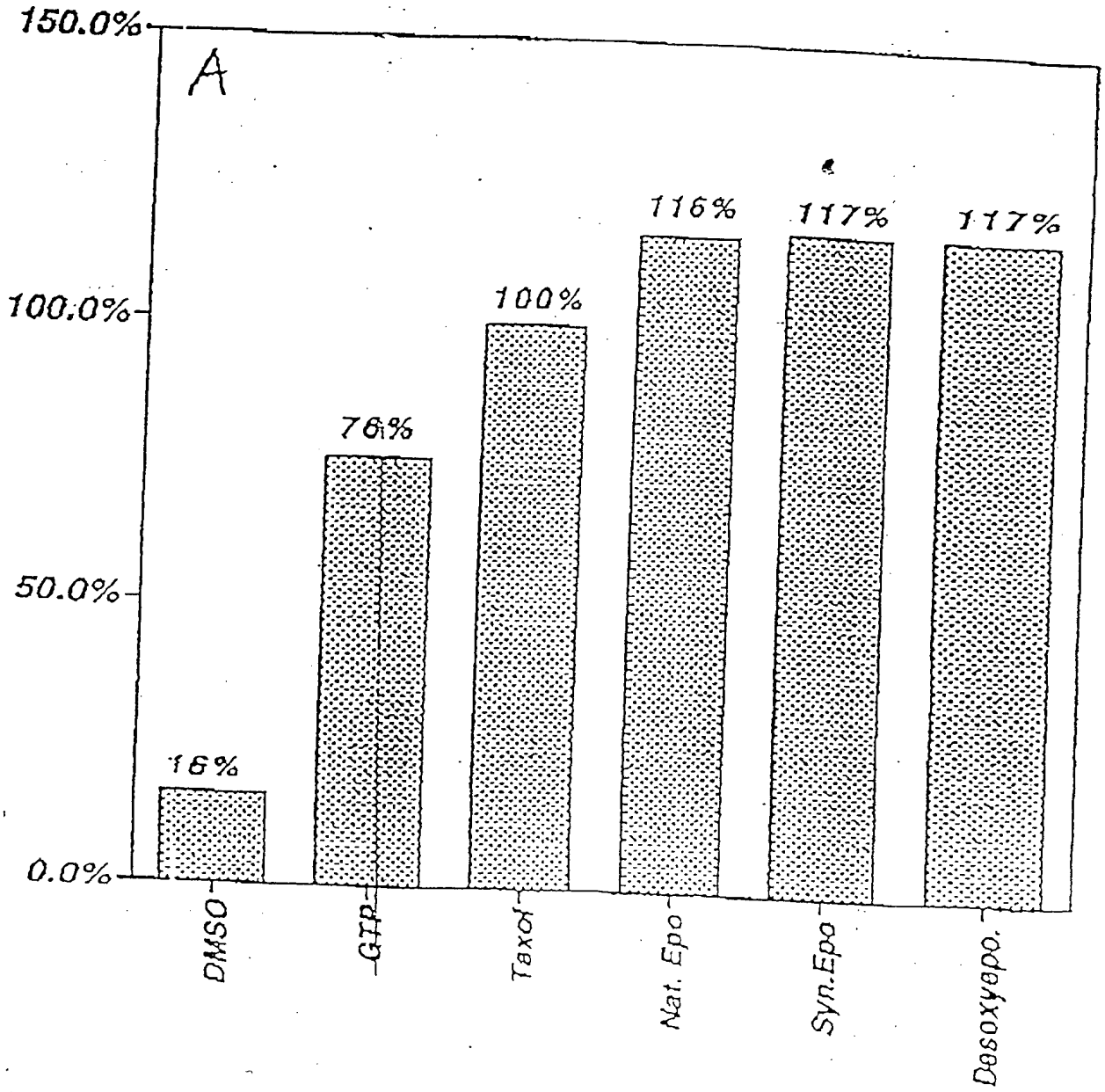


Figure 10

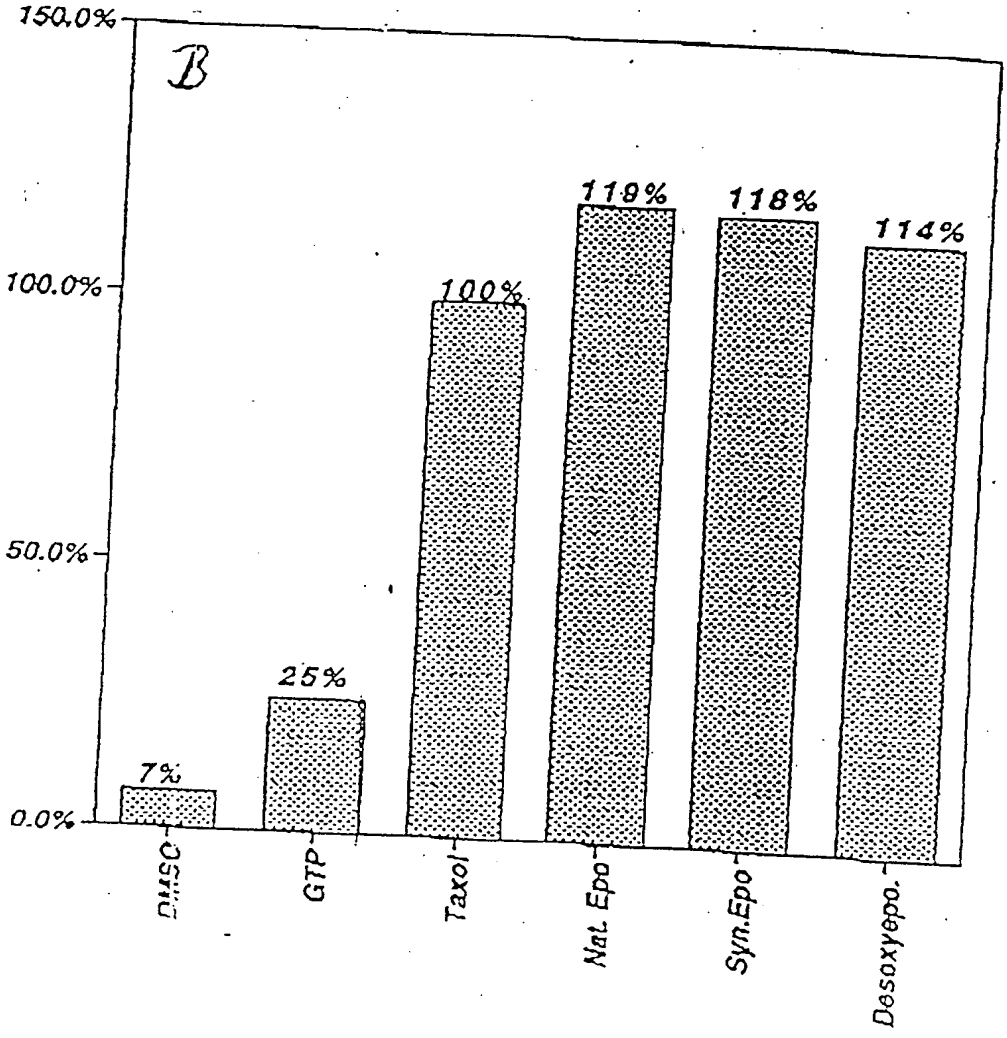
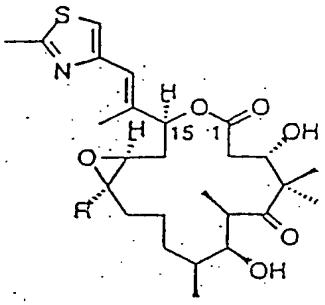


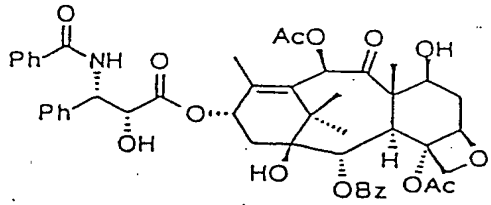
Figure 11

(A)



R = H; epothilone A
R = CH_3; epothilone B

(B)



1A: Taxol™

Figure 12

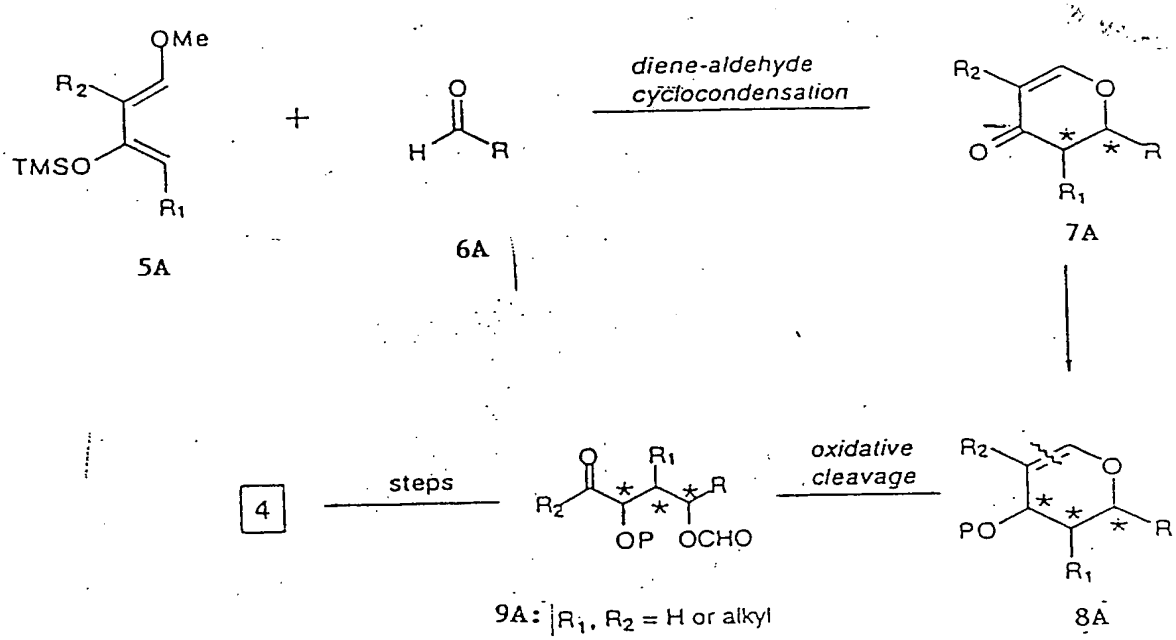


Figure 13

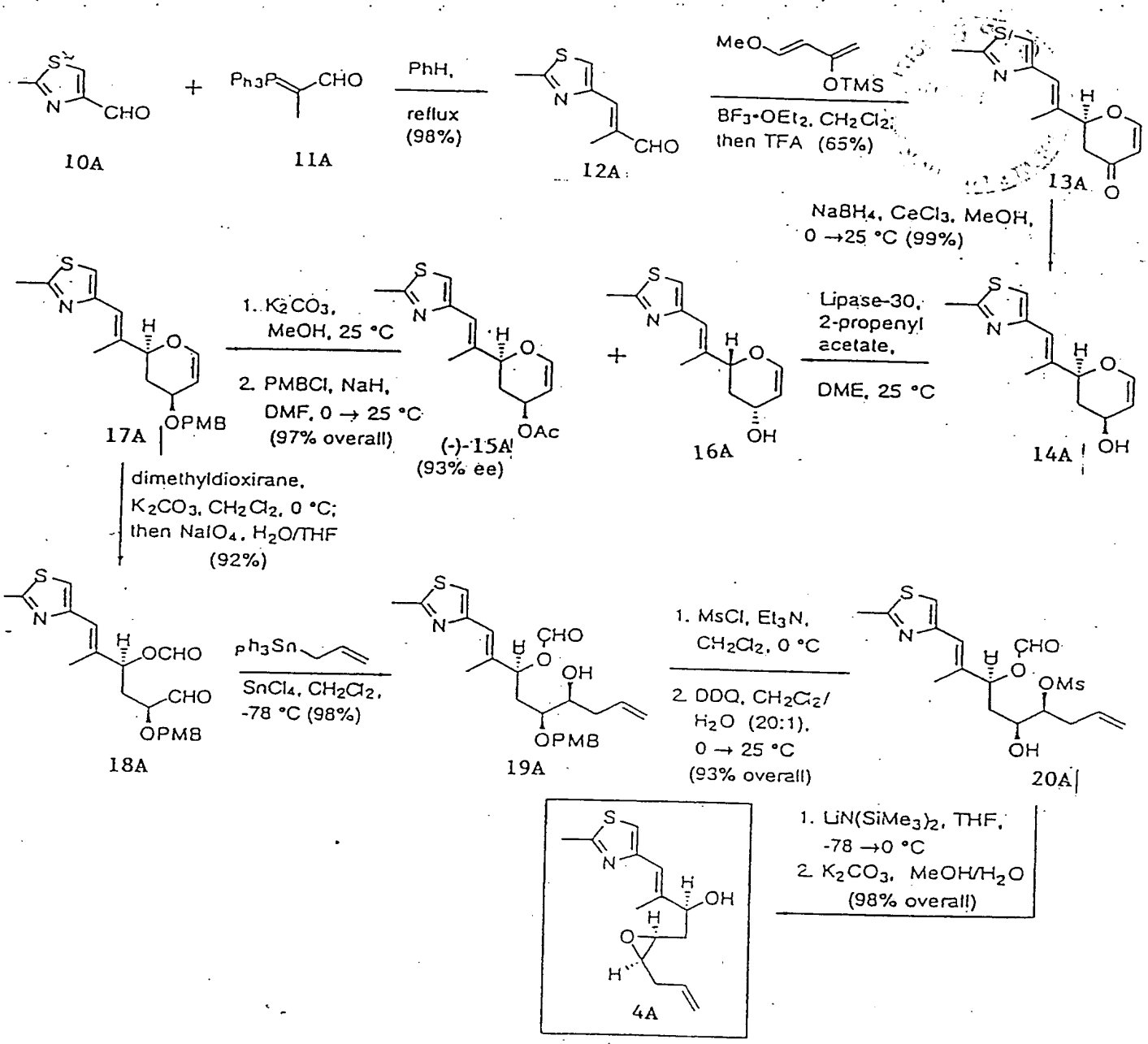

10A
11A
PhH, reflux (98%)
12A
MeO, OTMS
BF3•OEt2, CH2Cl2; then TFA (65%)
13A
NaBH4, CeCl3, MeOH, 0 →25 °C (99%)
17A
1. K2CO3, MeOH, 25 °C
2. PMBCl, NaH, DMF, 0 → 25 °C (97% overall)
(-)-15A
(93% ee)
16A
Lipase-30, 2-propenyl acetate, DME, 25 °C
14A
dimethyldioxirane, K2CO3, CH2Cl2, 0 °C; then NaIO4, H2O/THF (92%)
18A
Ph3Sn
SnCl4, CH2Cl2, -78 °C (98%)
19A
1. MsCl, Et3N, CH2Cl2, 0 °C
2. DDQ, CH2Cl2/H2O (20:1), 0 → 25 °C (93% overall)
20A
1. LiN(SiMe3)2, THF, -78 →0 °C
2. K2CO3, MeOH/H2O (98% overall)
4A

Figure 14

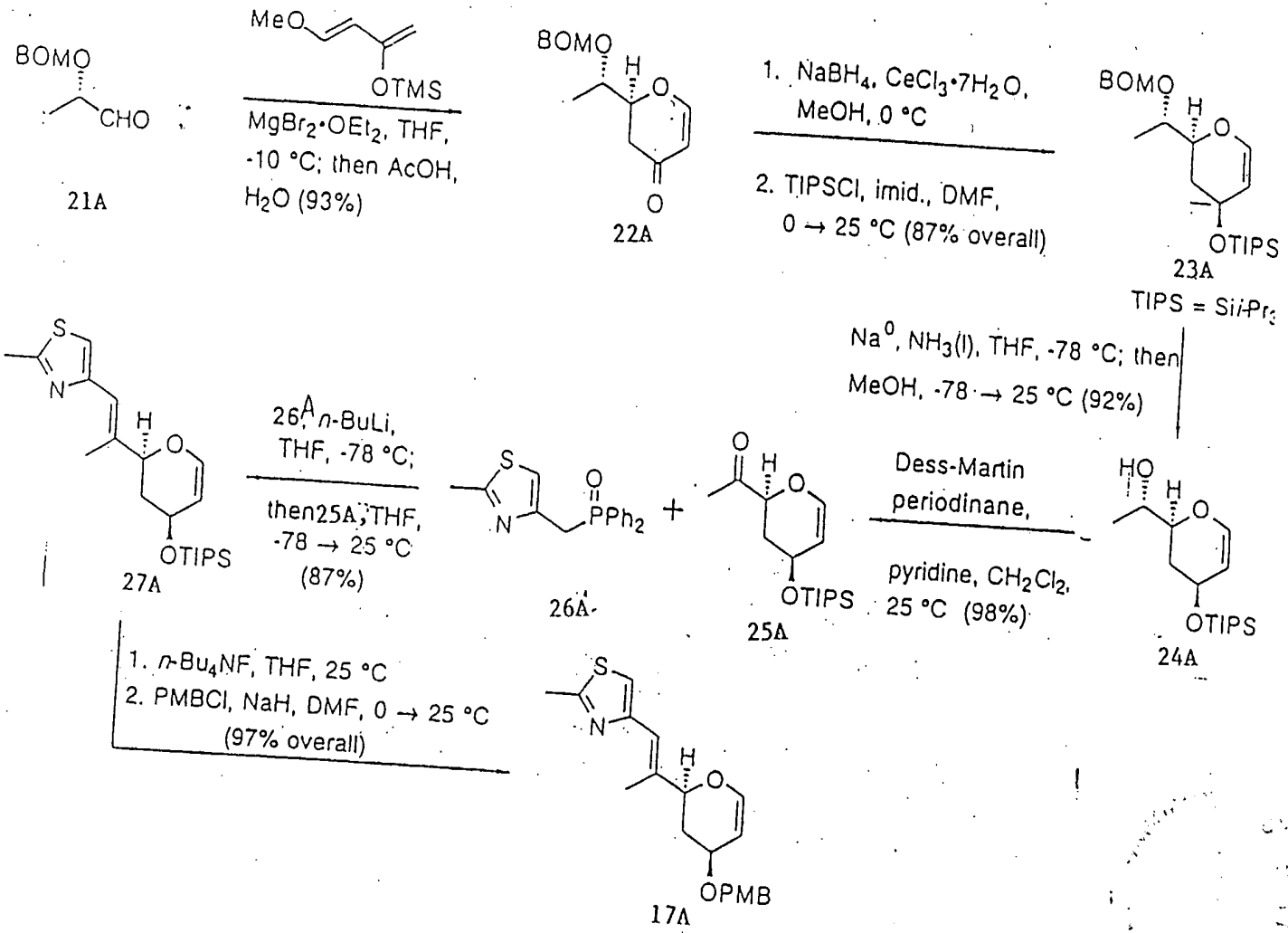
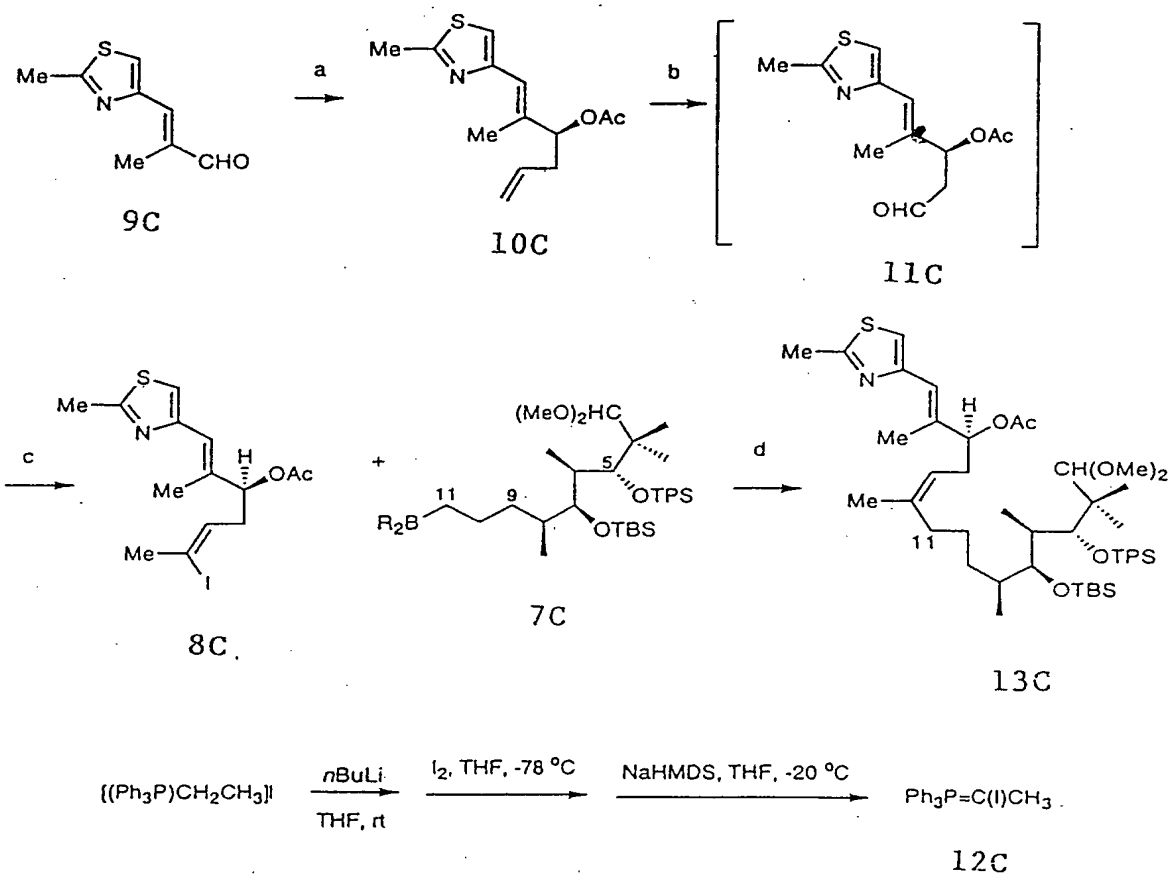

BOMO
CHO
21A
MeO
OTMS
MgBr2•OEt2, THF, -10 °C; then AcOH, H2O (93%)
22A
1. NaBH4, CeCl3•7H2O, MeOH, 0 °C
2. TIPSCl, imid., DMF, 0 → 25 °C (87% overall)
23A
TIPS = Si-i-Pr3
Na0, NH3(l), THF, -78 °C; then MeOH, -78 → 25 °C (92%)
24A
Dess-Martin periodinane, pyridine, CH2Cl2, 25 °C (98%)
25A
26A
n-BuLi, THF, -78 °C; then 25A, THF, -78 → 25 °C (87%)
27A
1. n-Bu4NF, THF, 25 °C
2. PMBCl, NaH, DMF, 0 → 25 °C (97% overall)
17A
OPMB

Figure 15



12C

Figure 16

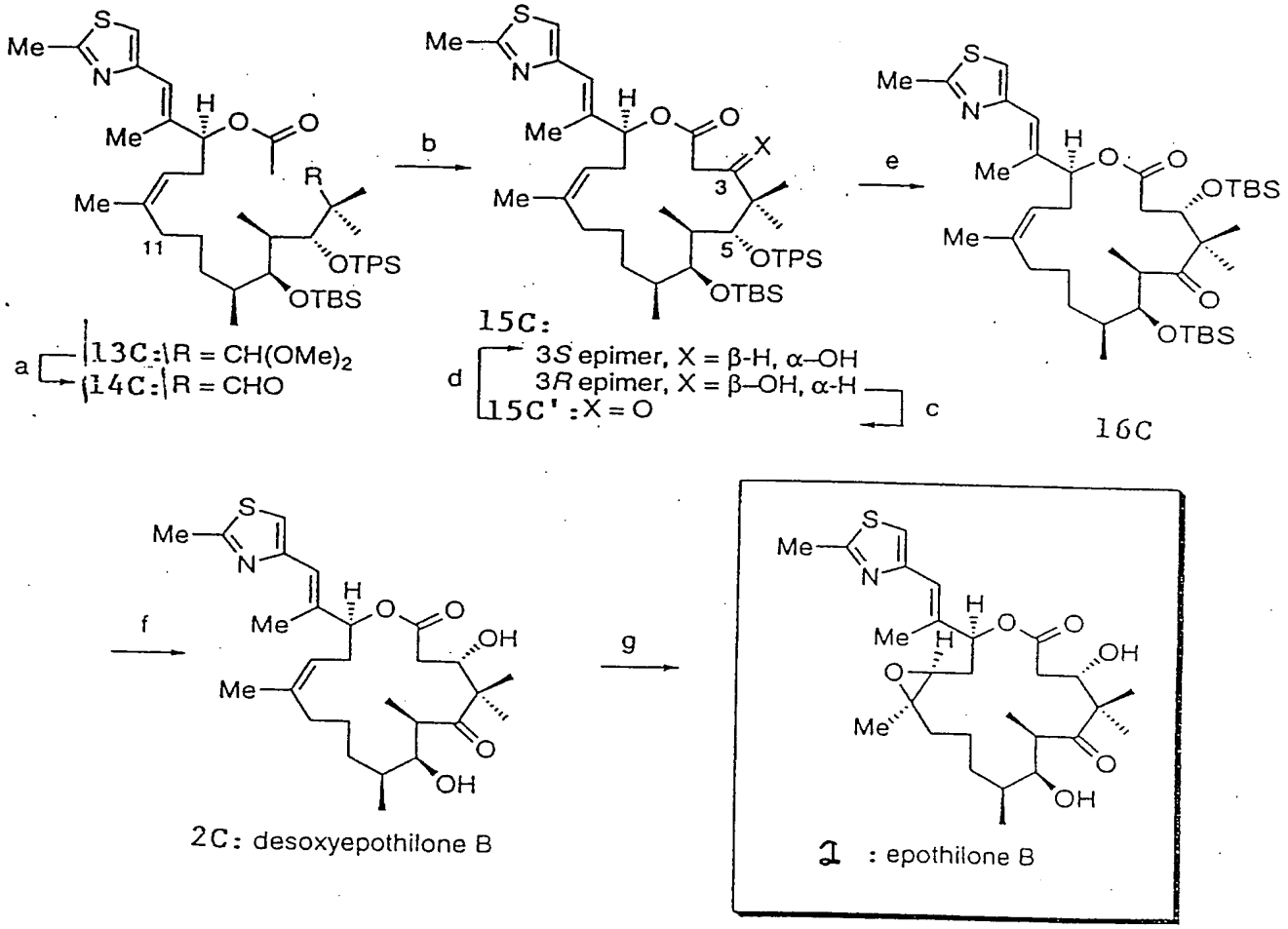


Figure 17

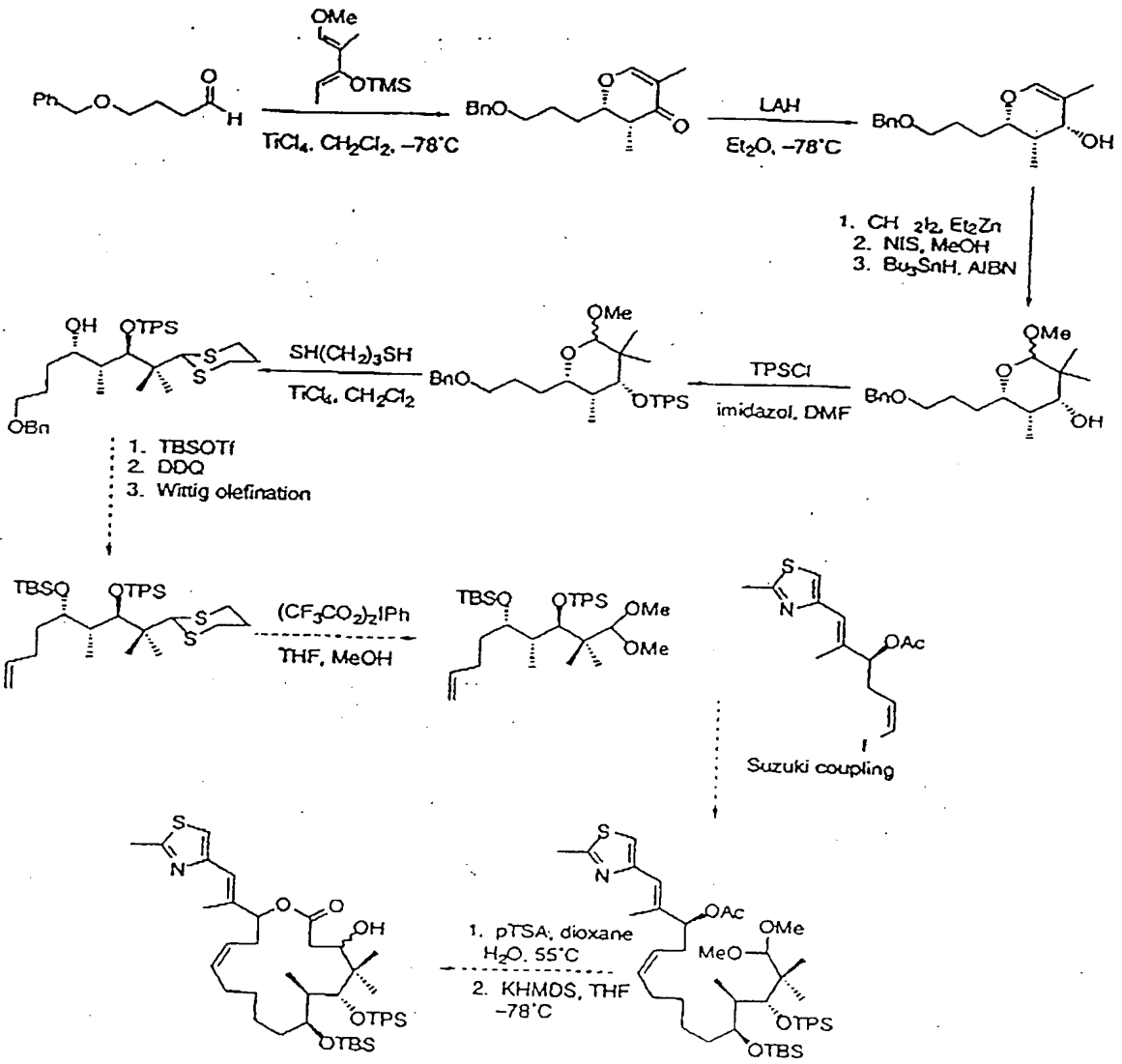


Figure 18

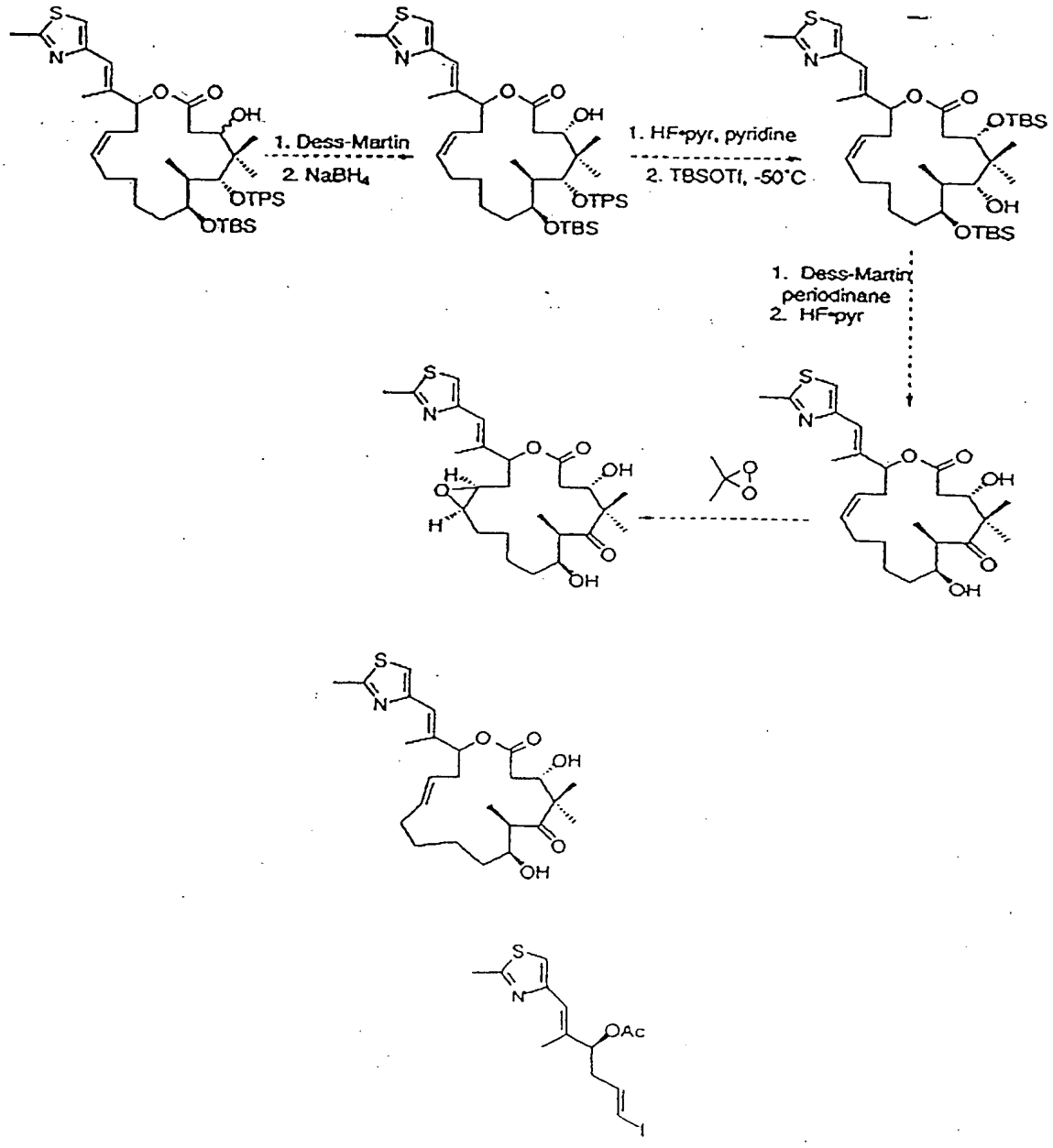
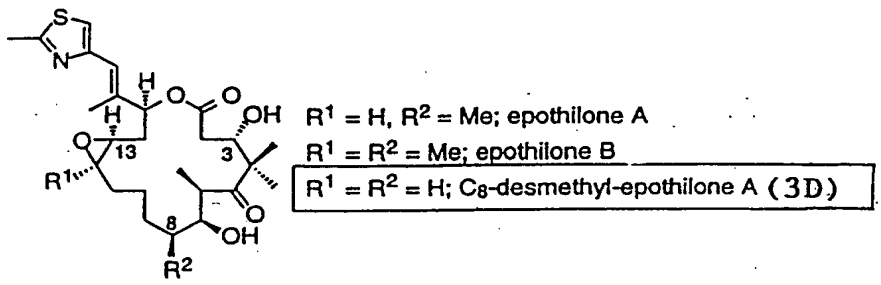


Figure 19


R1 = H, R2 = Me; epothilone A
R1 = R2 = Me; epothilone B
R1 = R2 = H; C8-desmethyl-epothilone A (3D)

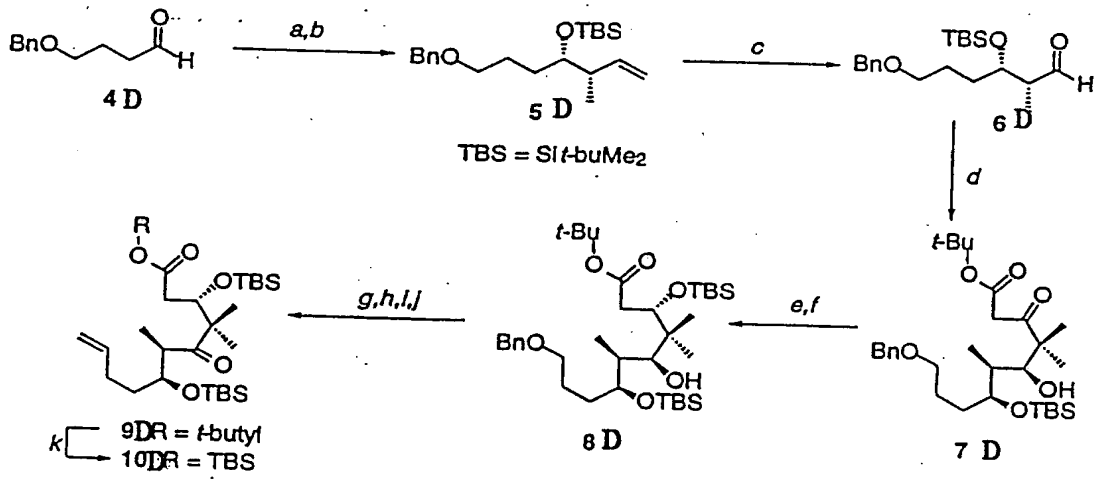

4 D
5 D
TBS = Si t-buMe2
6 D
7 D
8 D
9 D R = t-butyl
10 D R = TBS
a,b
c
d
e,f
g,h,i,j
k

FIGURE 20

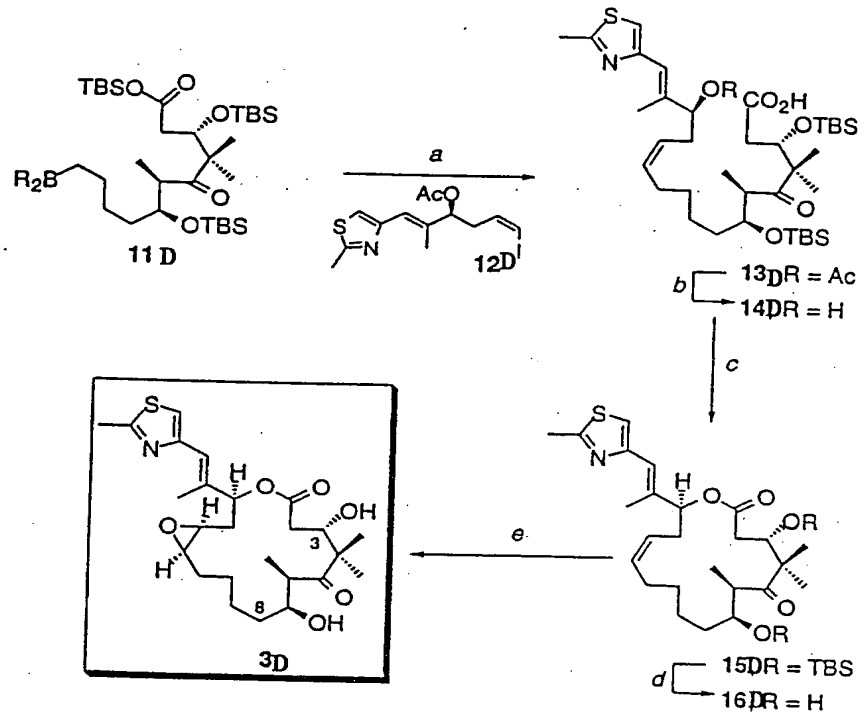


FIGURE 21

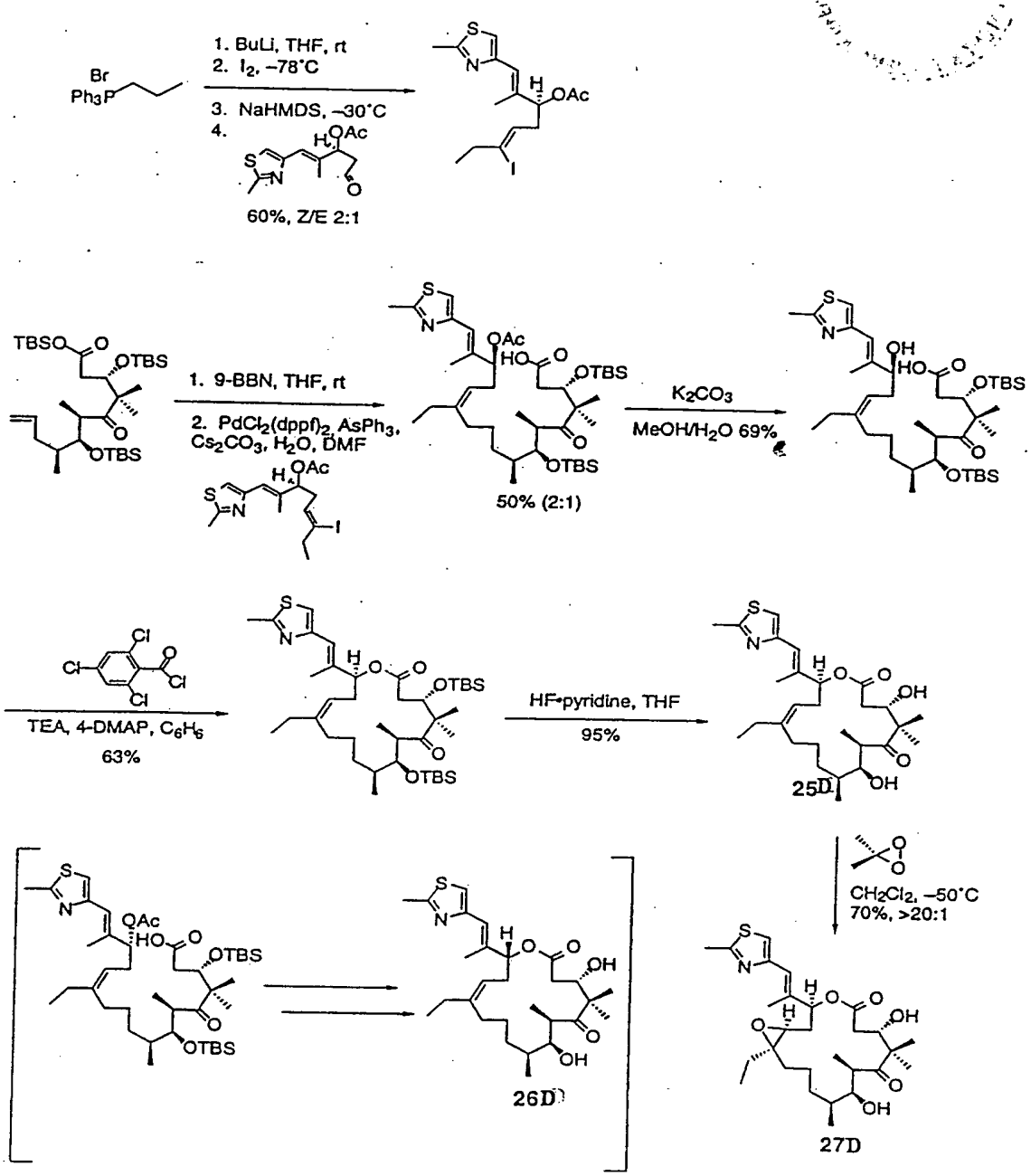

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
50% (2:1)
K2CO3
MeOH/H2O 69%
TEA, 4-DMAP, C6H6
63%
HF•pyridine, THF
95%
25D
CH2Cl2, –50°C
70%, >20:1
26D
27D

FIGURE 22

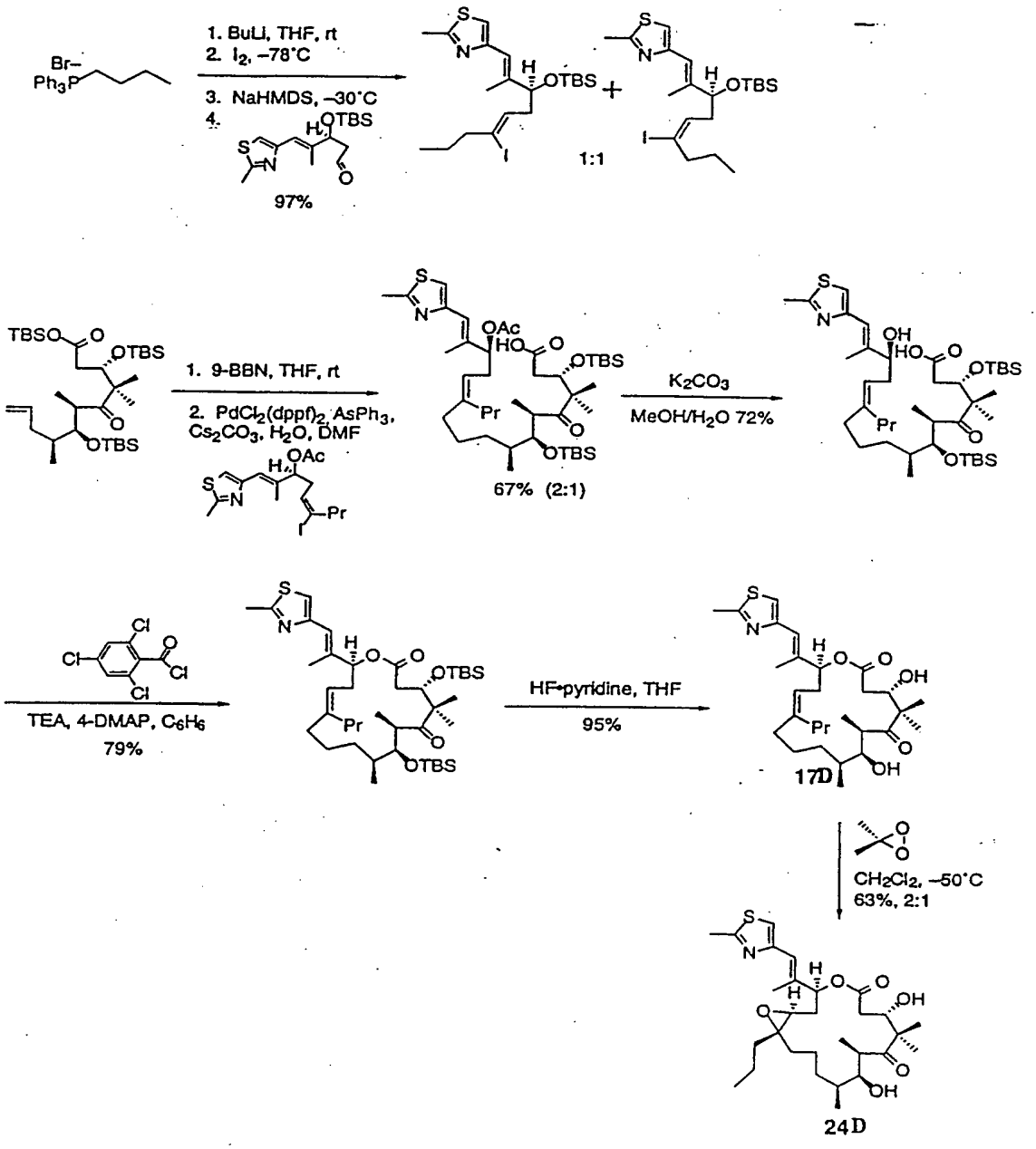


FIGURE 23

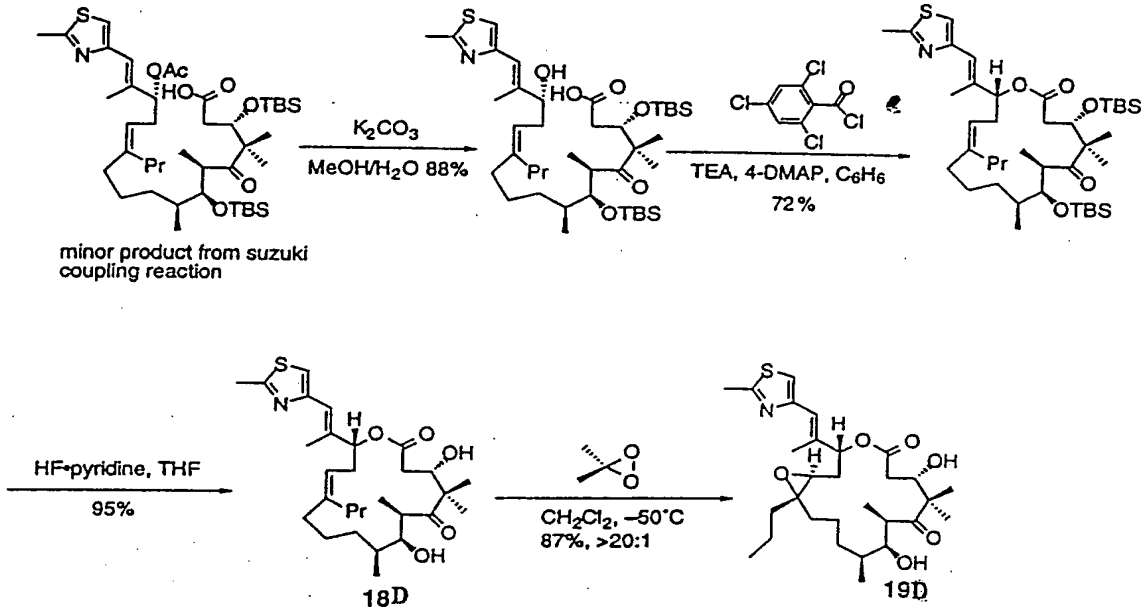

OAc
HO
OTBS
Pr
OTBS
minor product from suzuki coupling reaction
K_2CO_3
MeOH/H_2O 88%
OH
HO
OTBS
Pr
OTBS
Cl
Cl
Cl
O
Cl
TEA, 4-DMAP, C_6H_6
72%
H
O
OTBS
Pr
OTBS
HF•pyridine, THF
95%
H
O
OH
Pr
OH
18D
CH_2Cl_2, –50°C
87%, >20:1
H
O
OH
19D

FIGURE 24

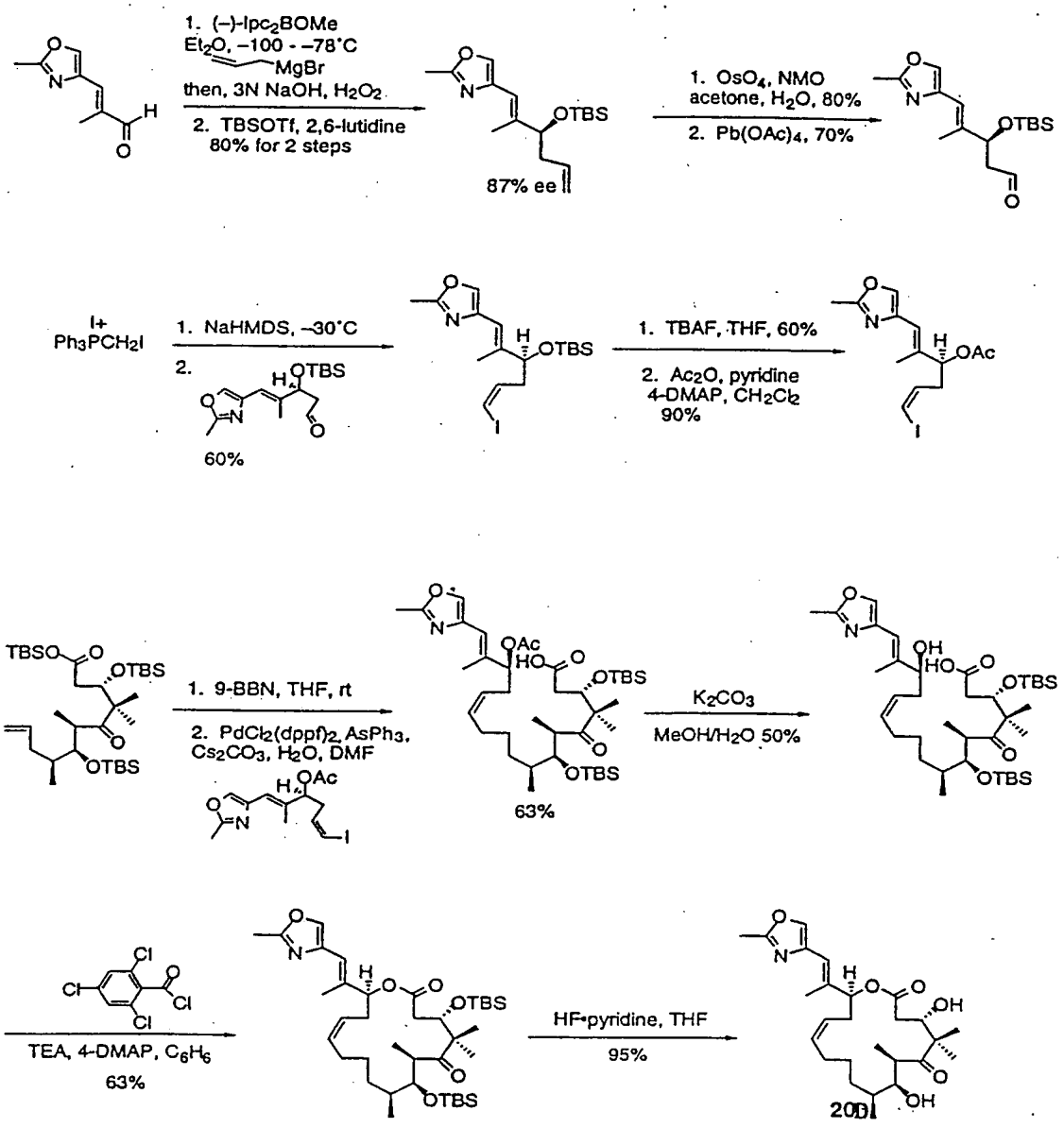


FIGURE 25

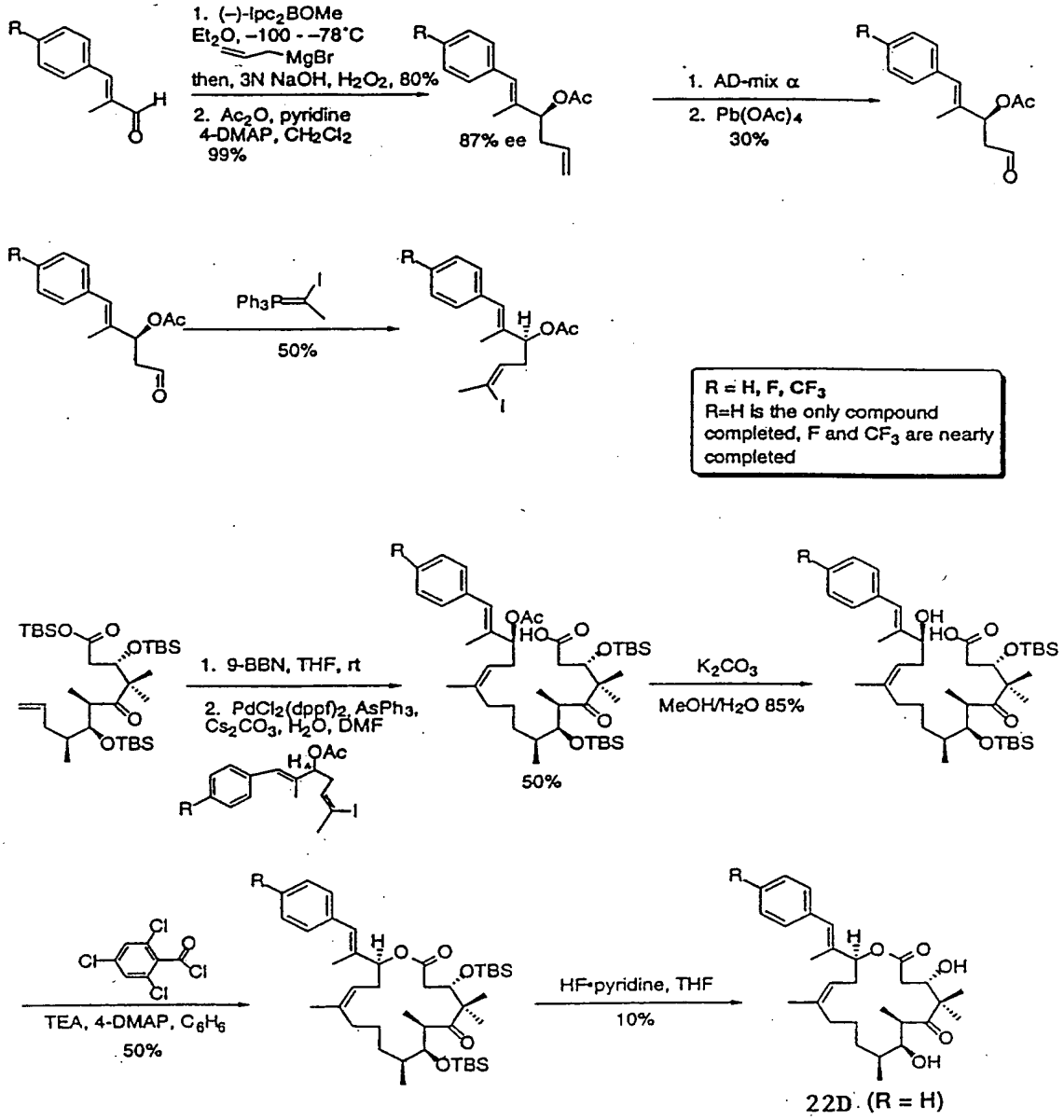


FIGURE 26

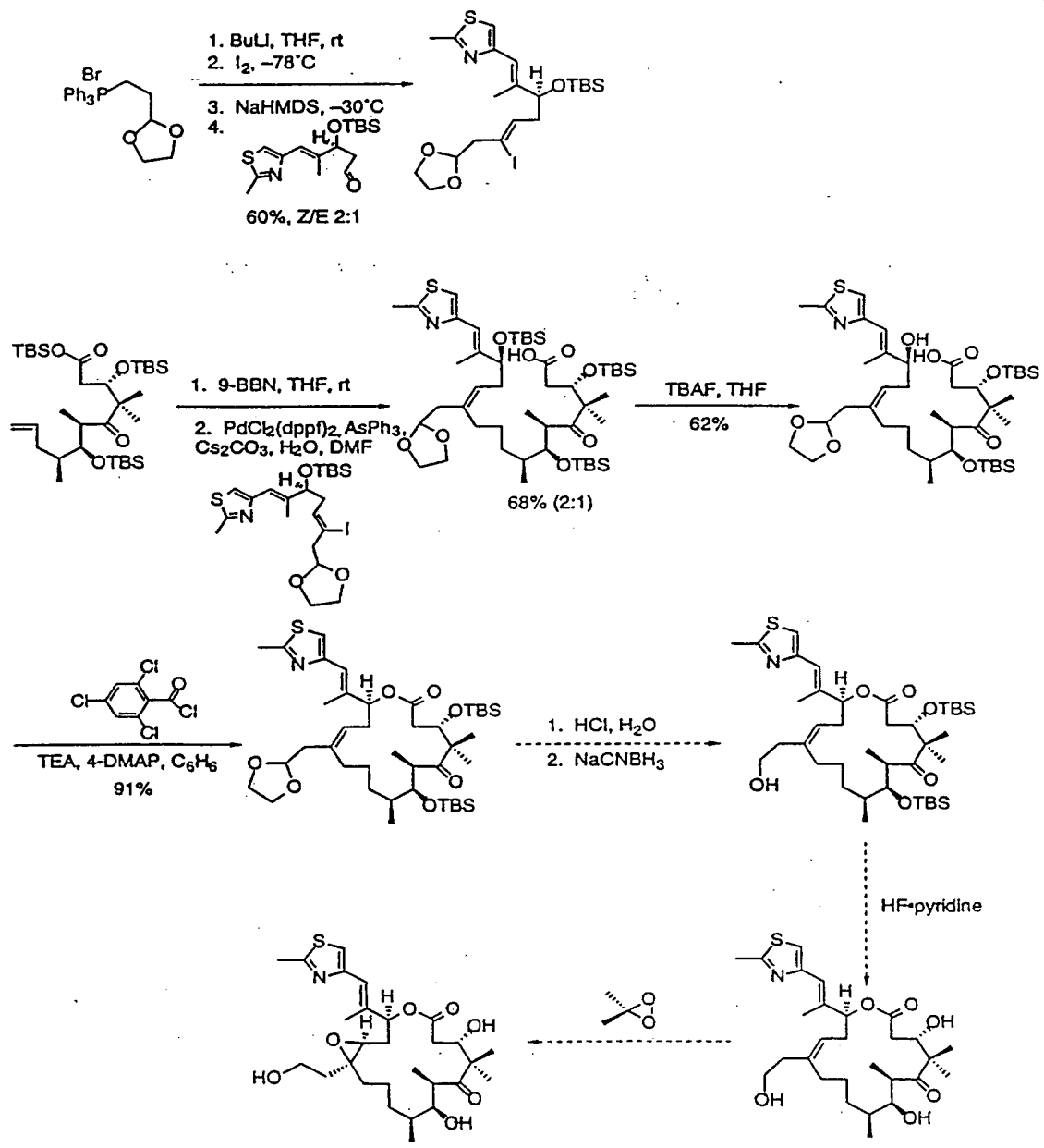
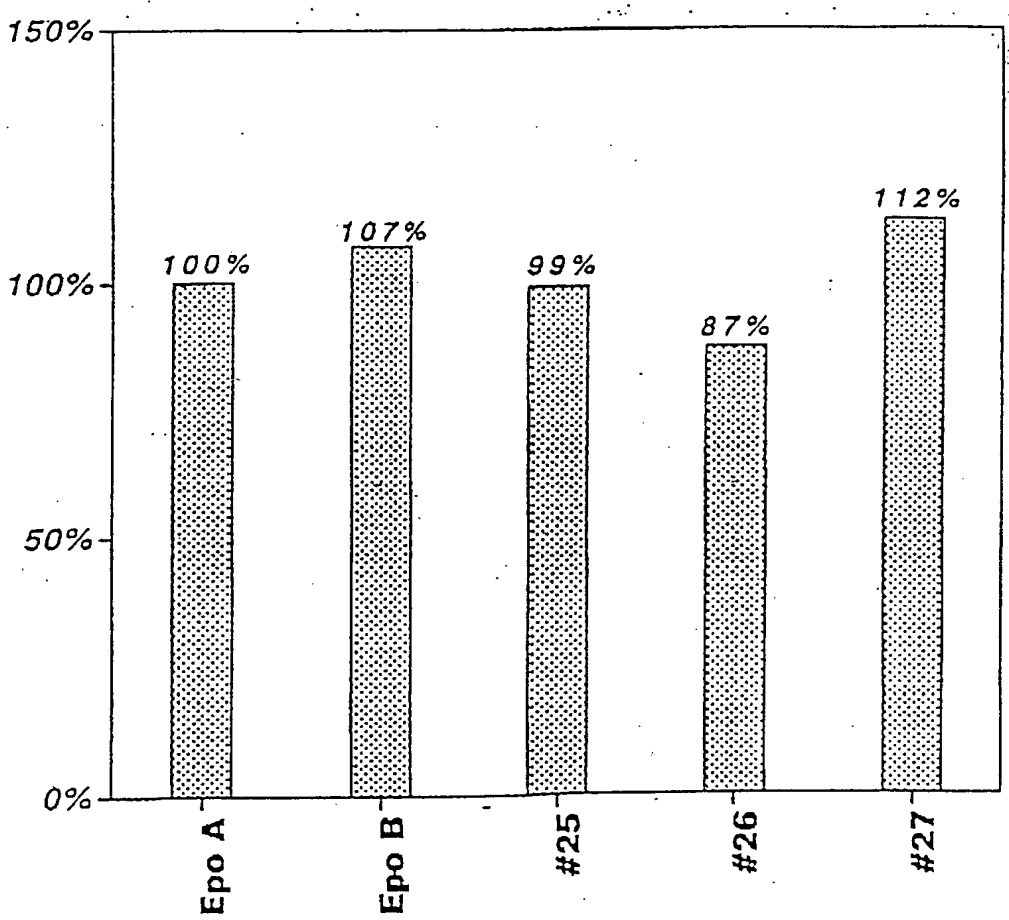

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
68% (2:1)
TBAF, THF
62%
TEA, 4-DMAP, C6H6
91%
1. HCl, H2O
2. NaCNBH3
HF•pyridine

FIGURE 27


150%
100%
50%
0%
100%
107%
99%
87%
112%
Epo A
Epo B
#25
#26
#27

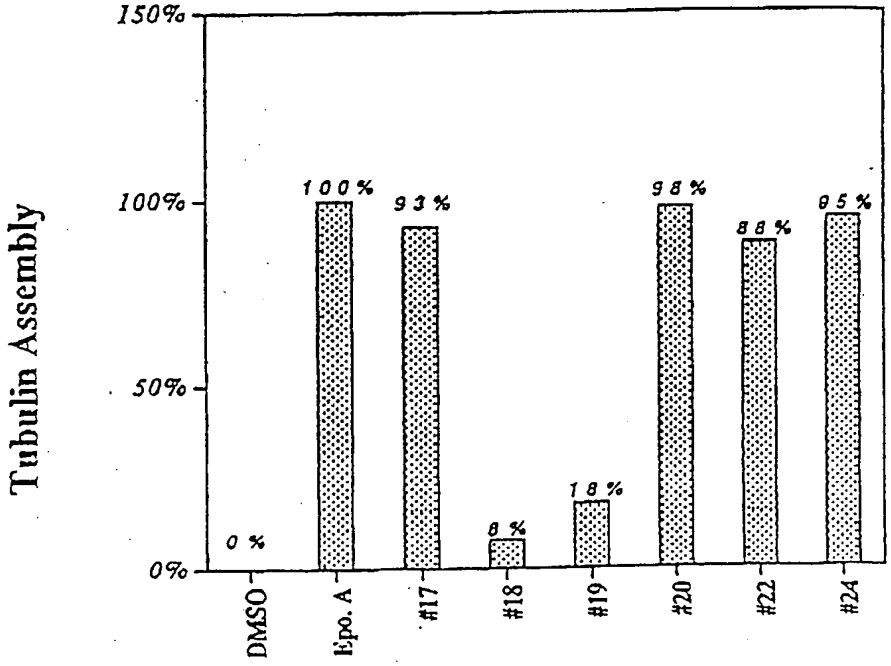
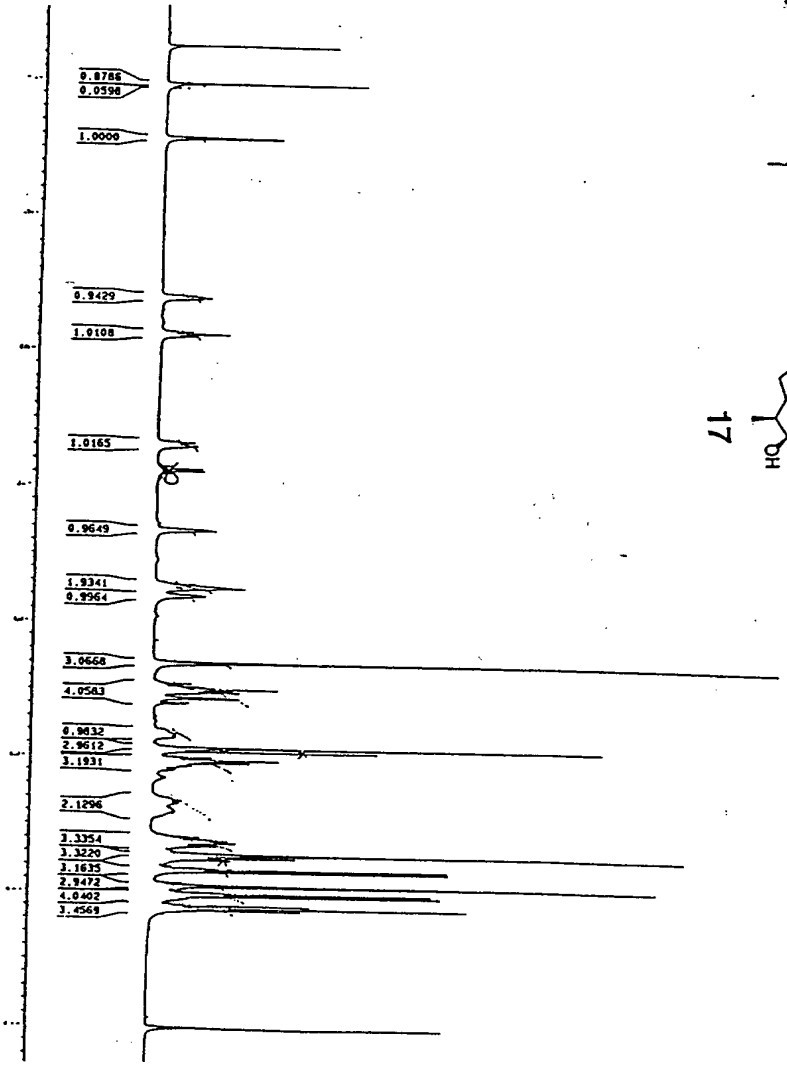

Tubulin Assembly
150%
100%
50%
0%
0 %
100%
93%
8%
18%
98%
88%
95%
DMSO
Epo. A
#17
#18
#19
#20
#22
#24

FIGURE 28


0.8786
0.0598
1.0000
0.9429
1.0108
1.0165
0.9649
1.0341
0.9964
3.0668
4.0583
0.9832
2.9612
3.1931
2.1296
3.3354
3.3220
3.1635
2.9472
4.0402
3.4569

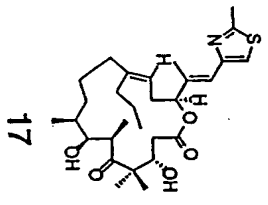
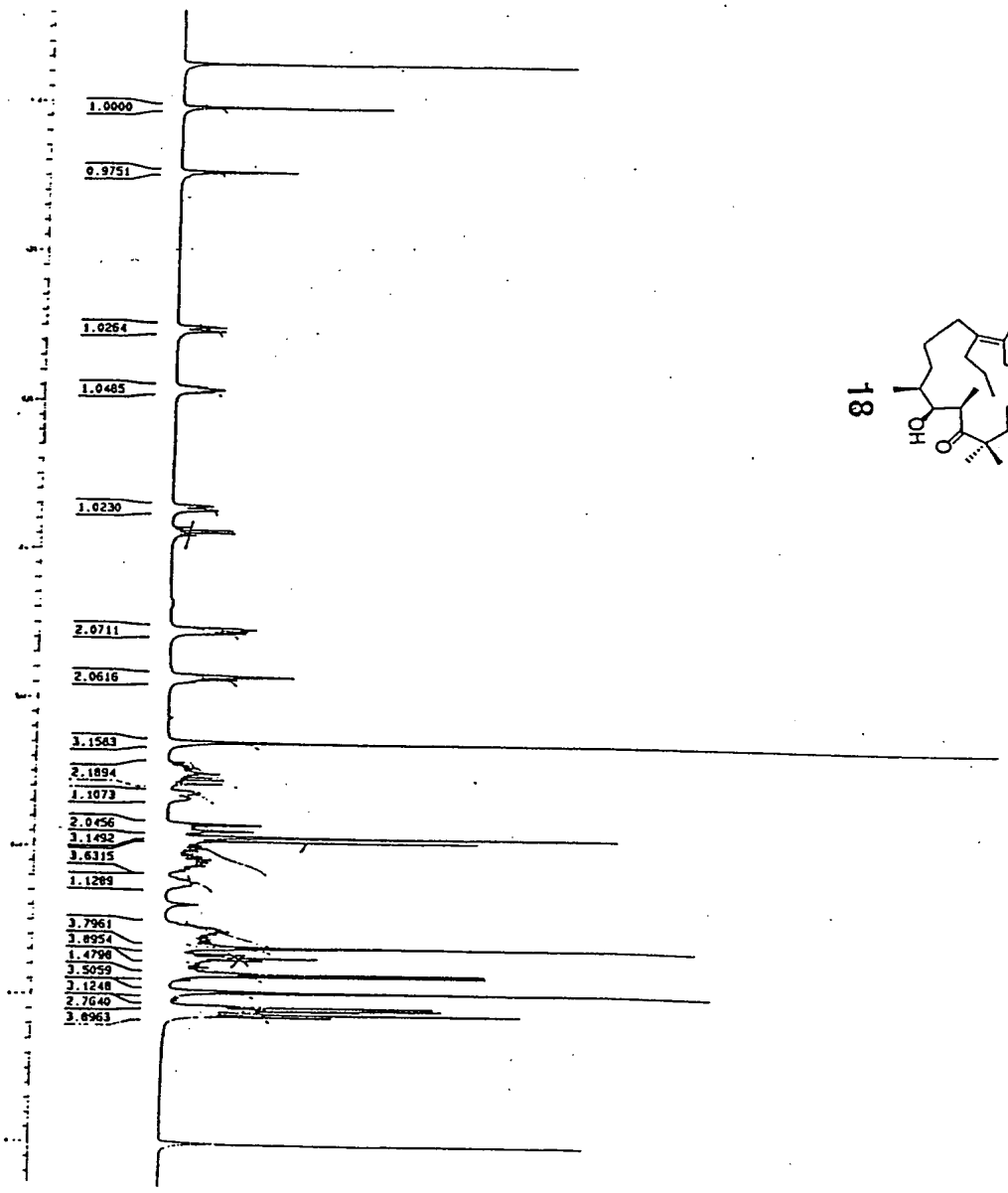

17
HO
O
H
N
S
O
O
HO

FIGURE 29


1.0000
0.9751
1.0264
1.0485
1.0230
2.0711
2.0616
3.1563
2.1894
1.1073
2.0456
3.1492
3.6315
1.1289
3.7961
3.8954
1.4798
3.5059
3.1248
2.7640
3.6963

18

FIGURE 30

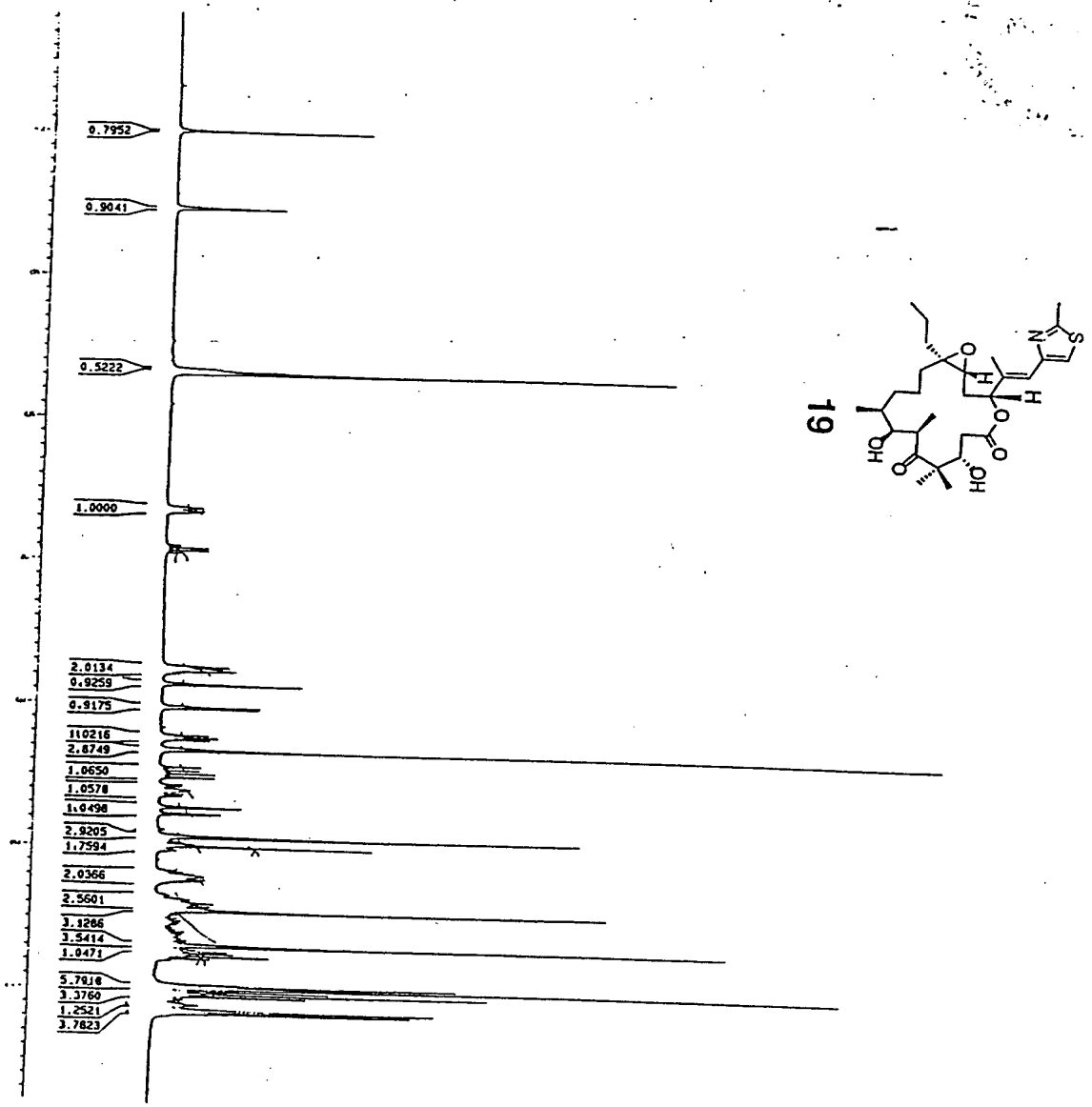

0.7952
0.9041
0.5222
1.0000
2.0134
0.9259
0.9175
1.0216
2.8749
1.0650
1.0578
1.0498
2.9205
1.7594
2.0366
2.5601
3.1286
3.5414
1.0471
5.7918
3.3760
1.2521
3.7823
19
HO
O
O
O
H
H
N
S
HO

FIGURE 31

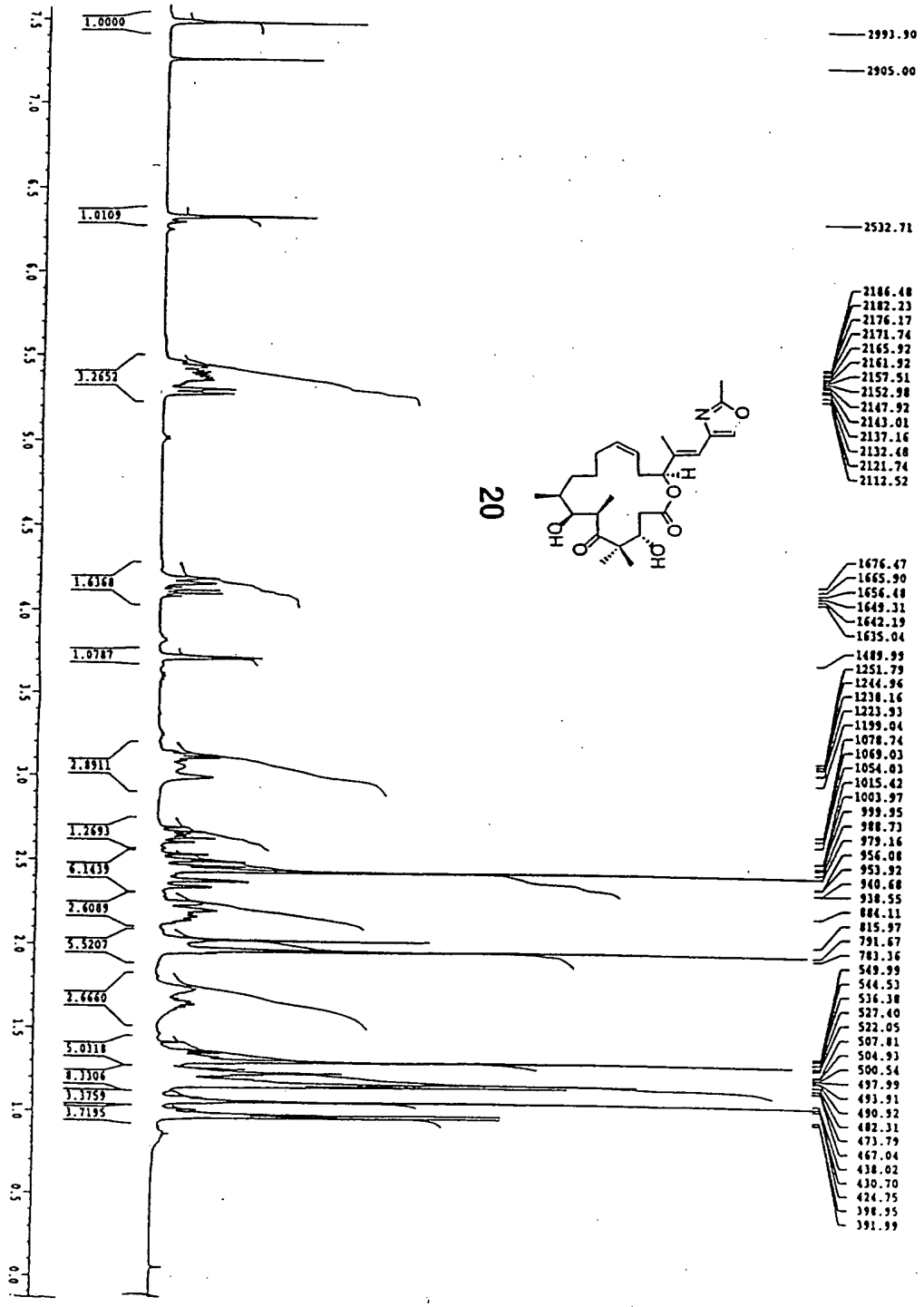


FIGURE 32

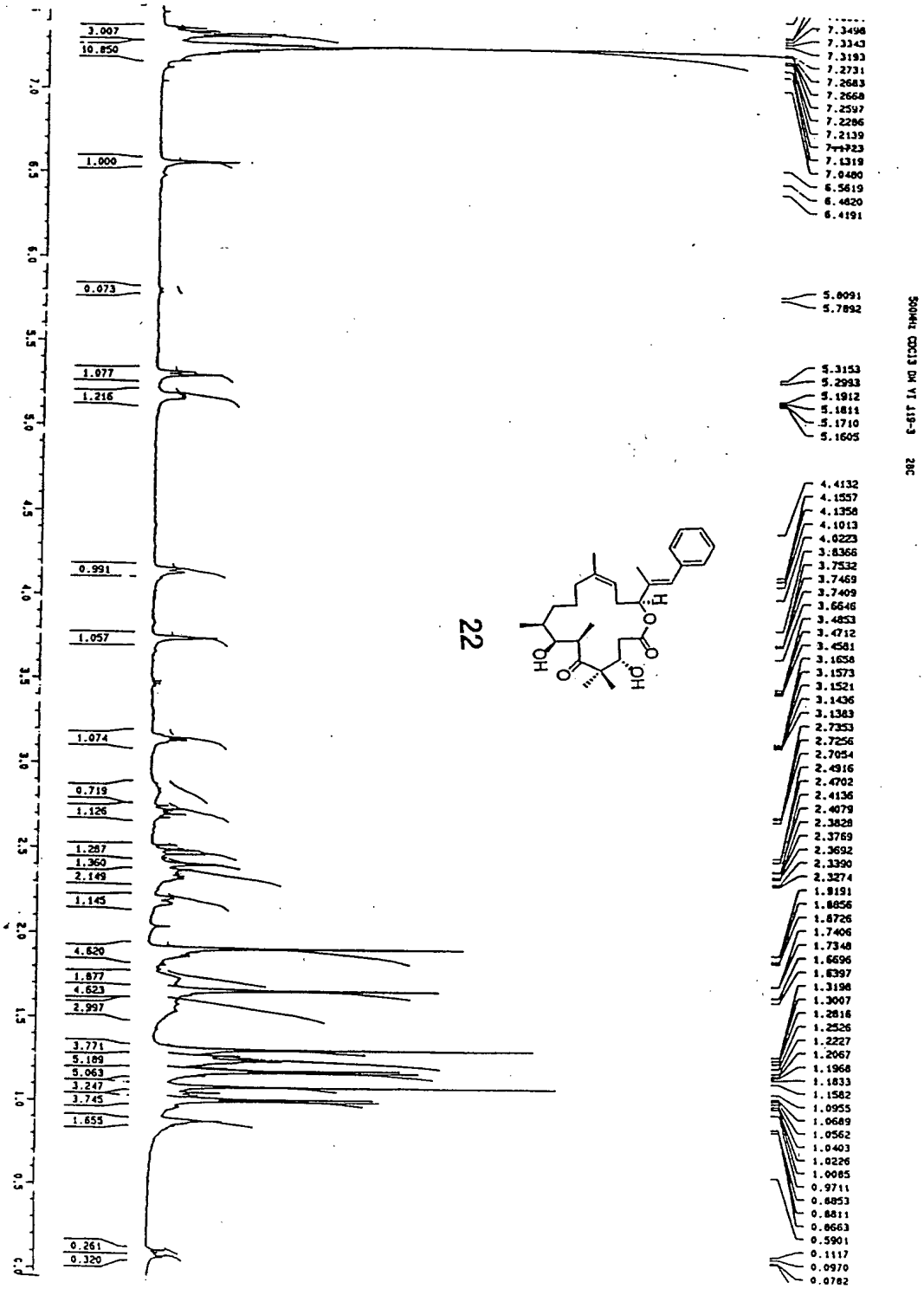


FIGURE 33

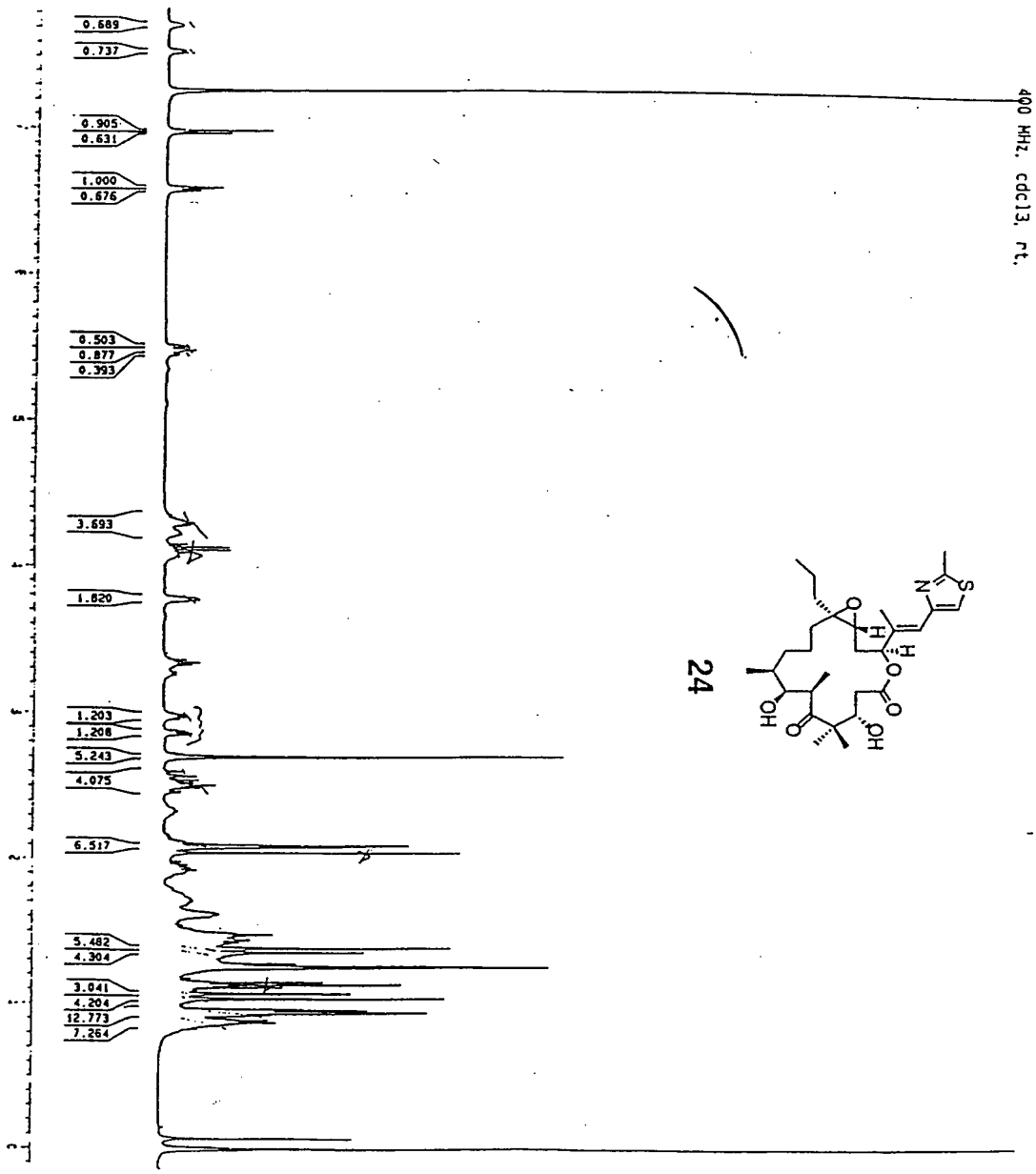

0.689
0.737
0.905
0.631
1.000
0.676
0.503
0.877
0.393
3.693
1.820
1.203
1.208
5.243
4.075
6.517
5.482
4.304
3.041
4.204
12.773
7.264
400 MHz, cdcl3, rt.
24
HO
HO
O
O
O
H
H
N
S

FIGURE 34

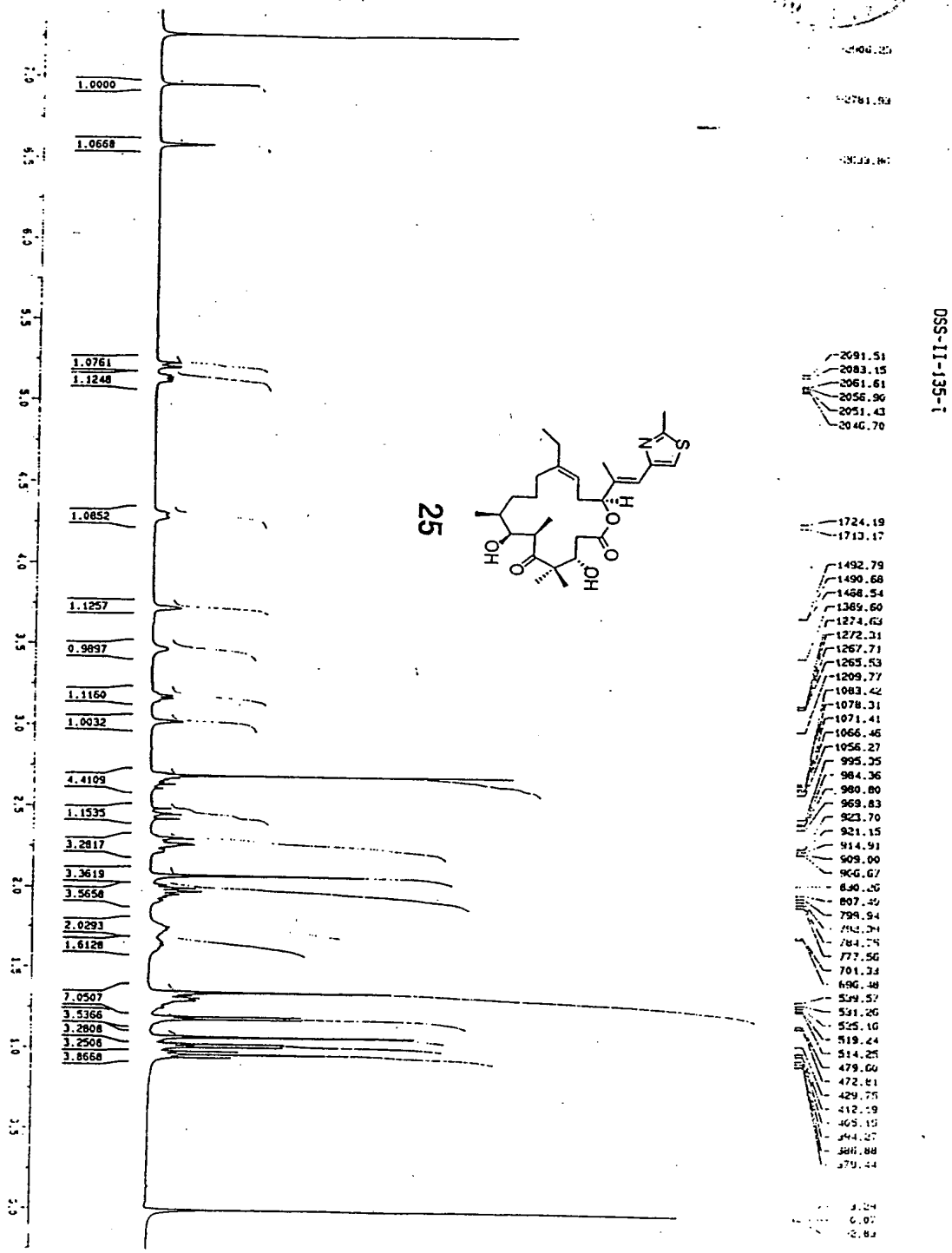


FIGURE 35

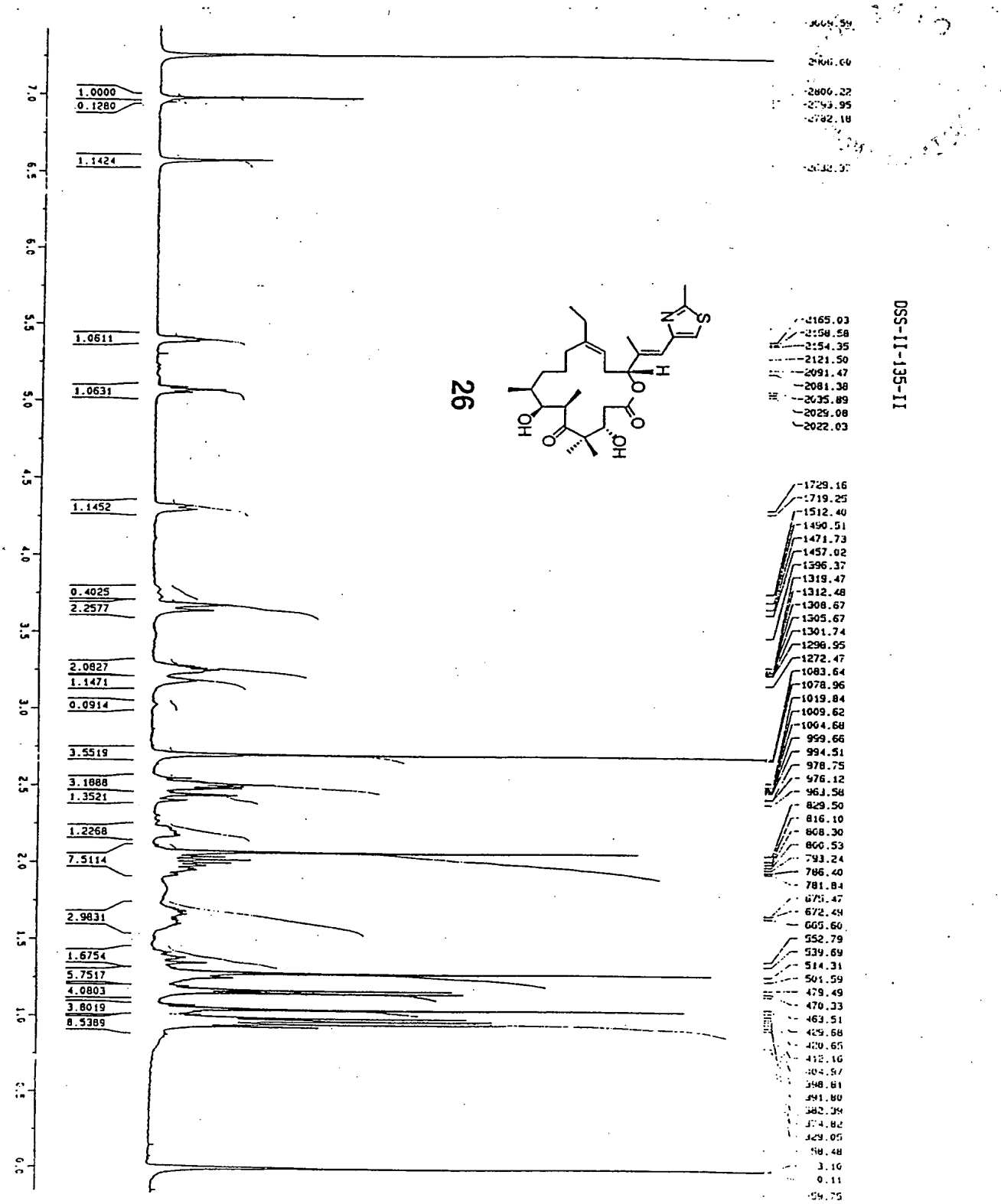

1.0000
0.1280
1.1424
1.0611
1.0631
1.1452
0.4025
2.2577
2.0827
1.1471
0.0914
3.5519
3.1888
1.3521
1.2268
7.5114
2.9831
1.6754
5.7517
4.0803
3.8019
8.5389
26
OH
O
N
S
OSS-II-135-II

FIGURE 36

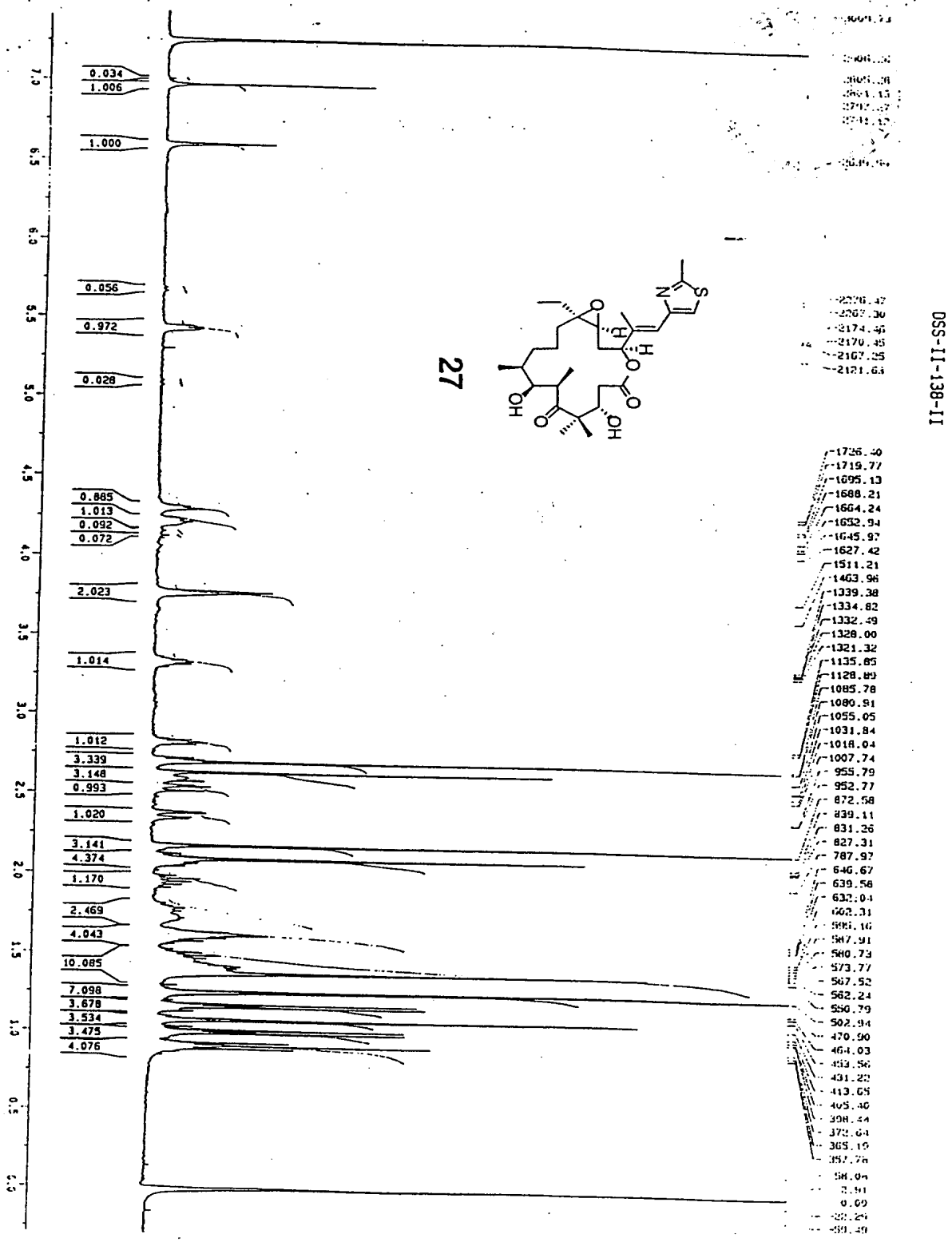

0.034
1.006
1.000
0.056
0.972
0.028
0.885
1.013
0.092
0.072
2.023
1.014
1.012
3.339
3.148
0.993
1.020
3.141
4.374
1.170
2.469
4.043
10.085
7.098
3.678
3.534
3.475
4.076
27
OSS-III-138-II

FIGURE 37

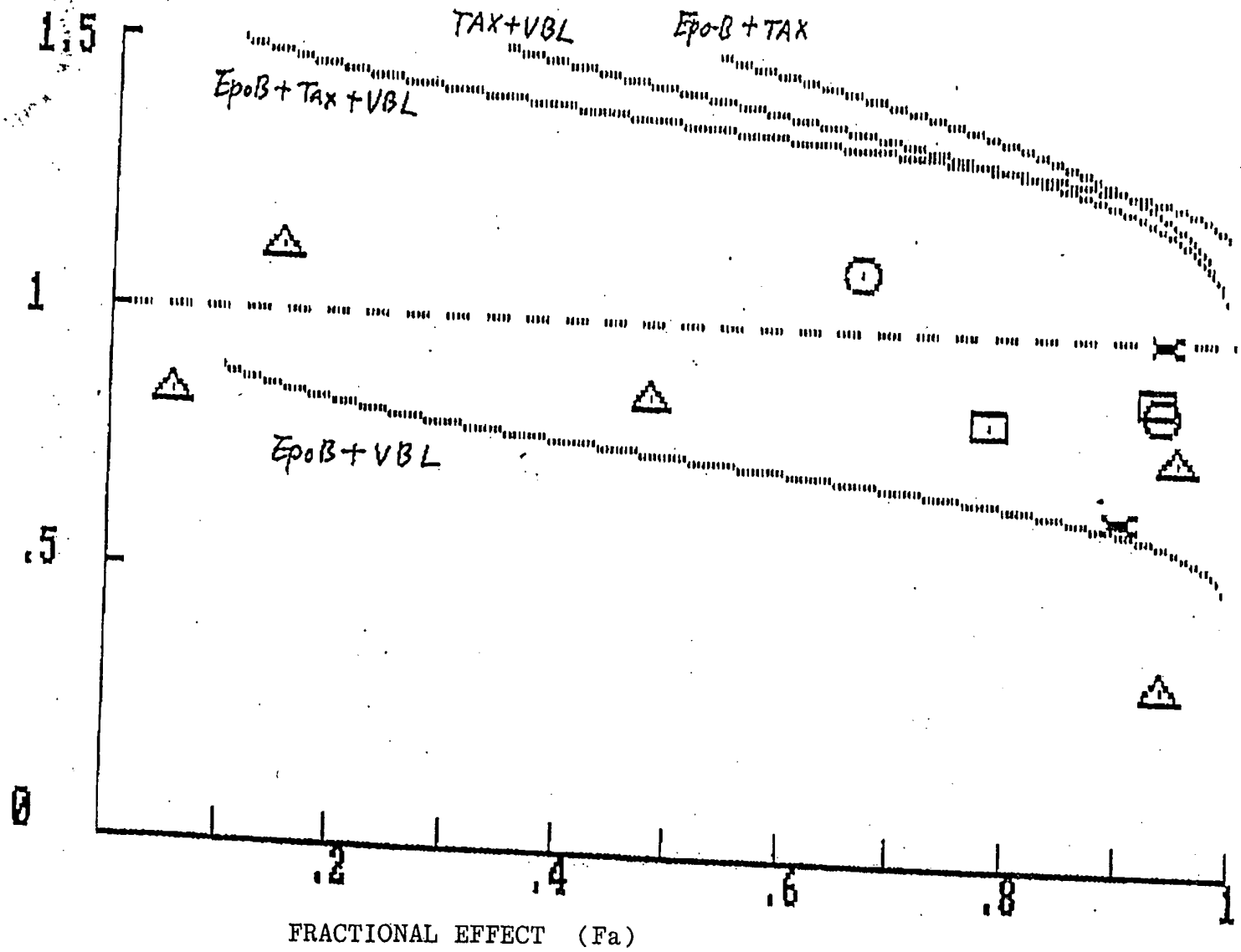
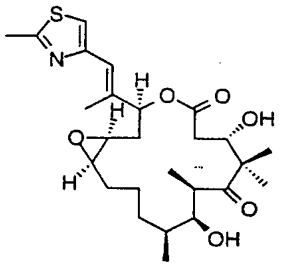
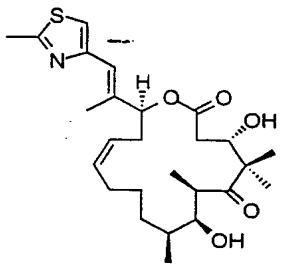


Figure 38

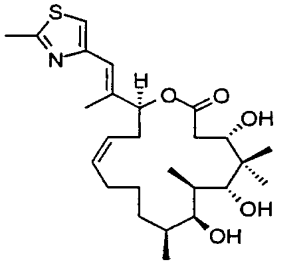


epothilone A
(0.0027)
[0.020]

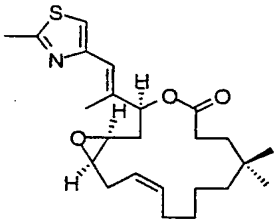


desoxyepothilone A

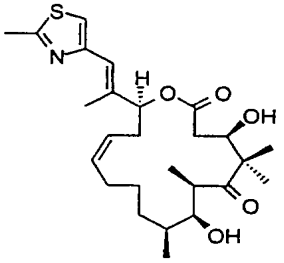
1
(0.022)
[0.012]



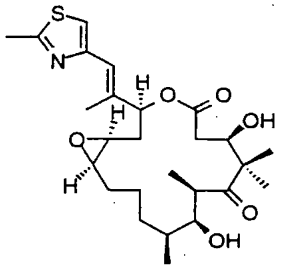
2
(14.23)
[6.28]



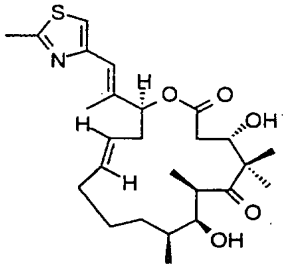
3
(271.1)
[22.4]



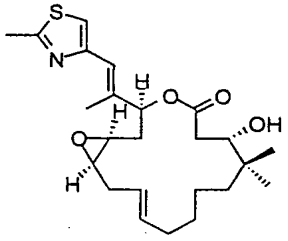
4
(2.12)
[43.0]



5
(>20)
[35.2]

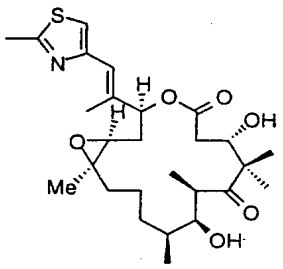


6
(0.052)
[0.035]



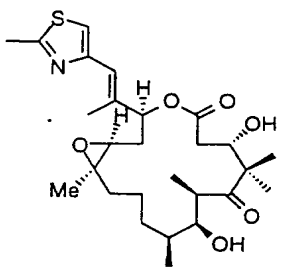
7
(7.36)
[9.82]

Fig. 39



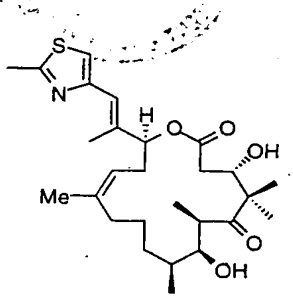
synthetic epothilone B

8
(0.00044)
[0.0026]



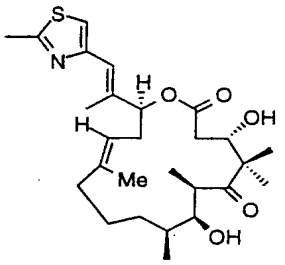
natural epothilone B

9
(0.00017)
[0.0012]

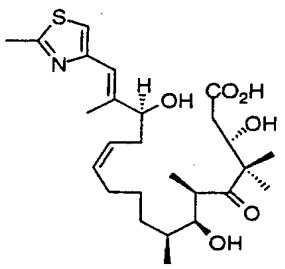


desoxyepothilone B

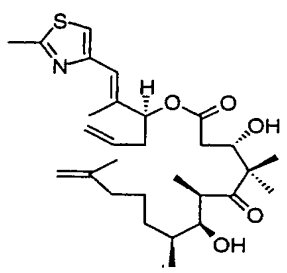
10
(0.0095)
[0.017]



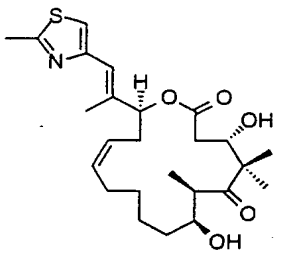
11
(0.090)
[0.262]



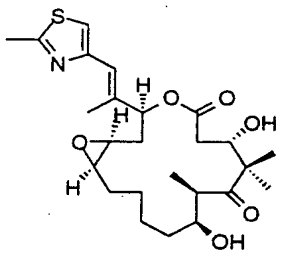
12
(0.79)
[>5]



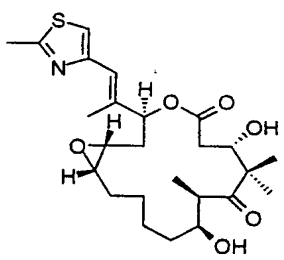
13
(11.53)
[5.63]



14
(5.42)
[5.75]

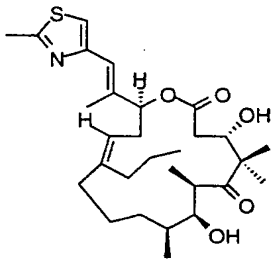


15
(0.96)
[5.95]

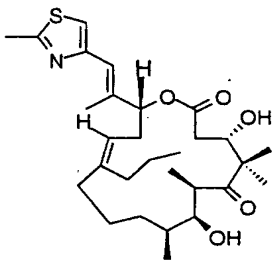


16
(7.47)
[16.48]

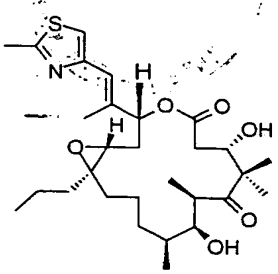
Fig. 40



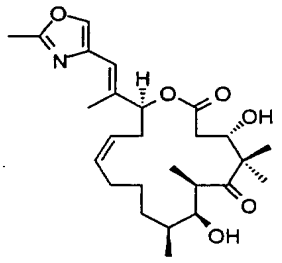
17
(0.090)
[0.254]



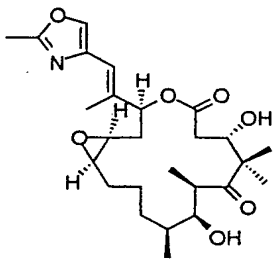
18
(1158)
[>720]



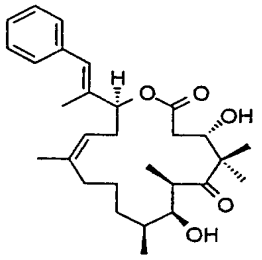
19
(0.96)
[>1.0]



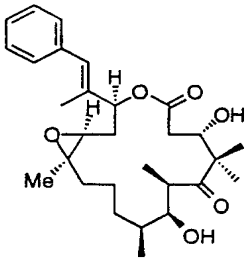
20
(0.030)
[0.049]



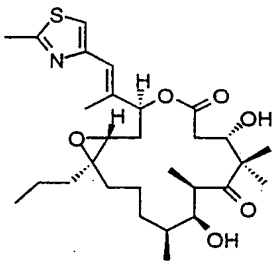
21



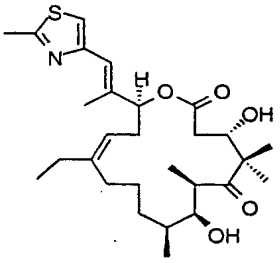
22
(0.098)
[0.146]



23

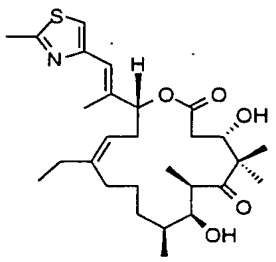


24
(0.0043)
[0.032]

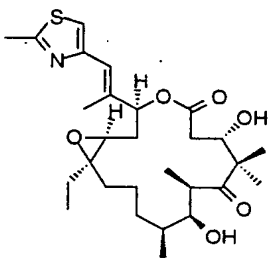


25
(0.021)
[0.077]

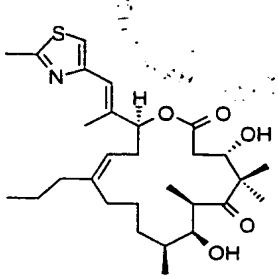
Fig. 41



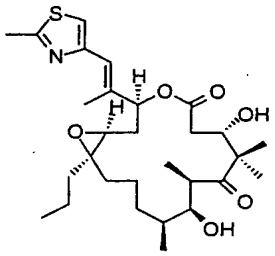
26
(0.055)
[0.197]



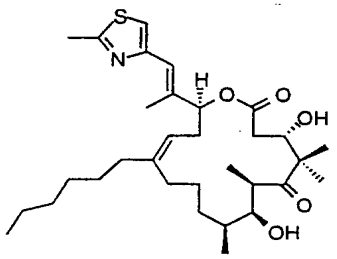
27
(0.0010)
[0.0072]



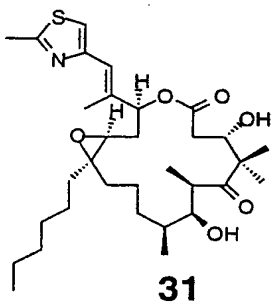
28
(0.039)
[0.067]



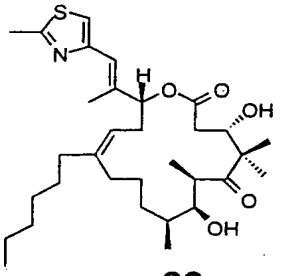
29
(0.0038)
[0.0064]



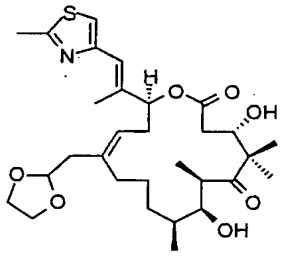
30
(0.044)
[0.108]



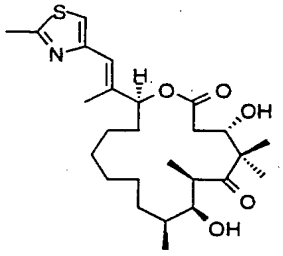
31
(0.027)
[0.049]



32
(0.063)
[0.380]

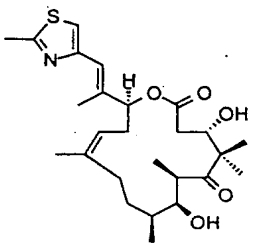


33
(0.0031)
[0.0093]

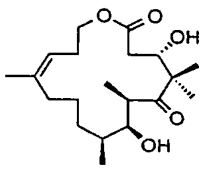


34
(0.143)
[0.276]

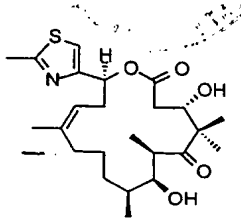
Fig. 42(A)



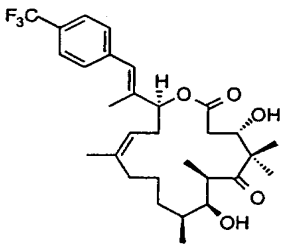
35
(>10)
[8.95]



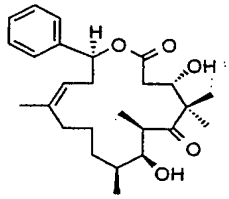
36
(234.5)
[>10]



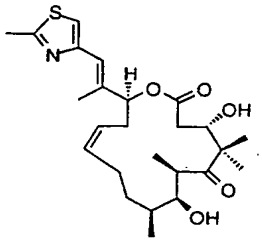
37
(3.25)
[1.20]



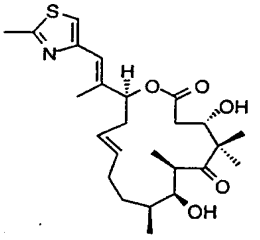
38
(0.254)
[>5.0]



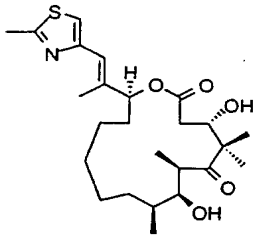
39
(1.80)
[>5.0]



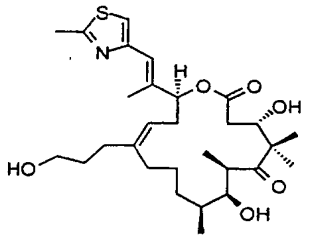
40
(36.9)
[47.3]



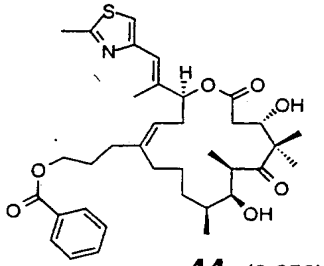
41
(60.1)
[59.2]



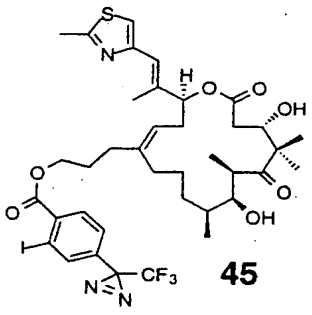
42
(7.41)
[12.9]



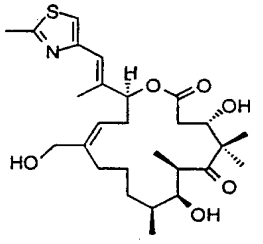
43
(0.0095)
[0.167]



44 (0.250)
[0.905]

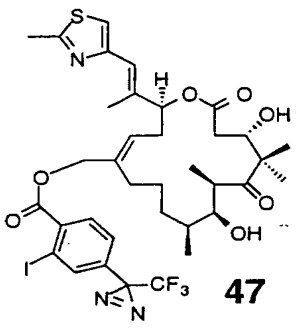


45

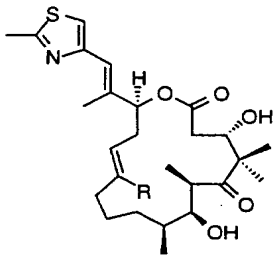


46 (0.049)
[>1.0]

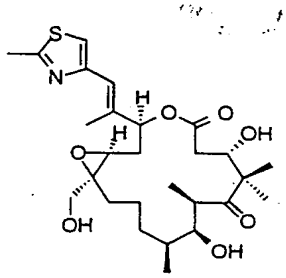
Fig. 42(B)



47



48 R = $(CH_2)_3OH$



49

Fig. 42(C)

Fig. 43(A)

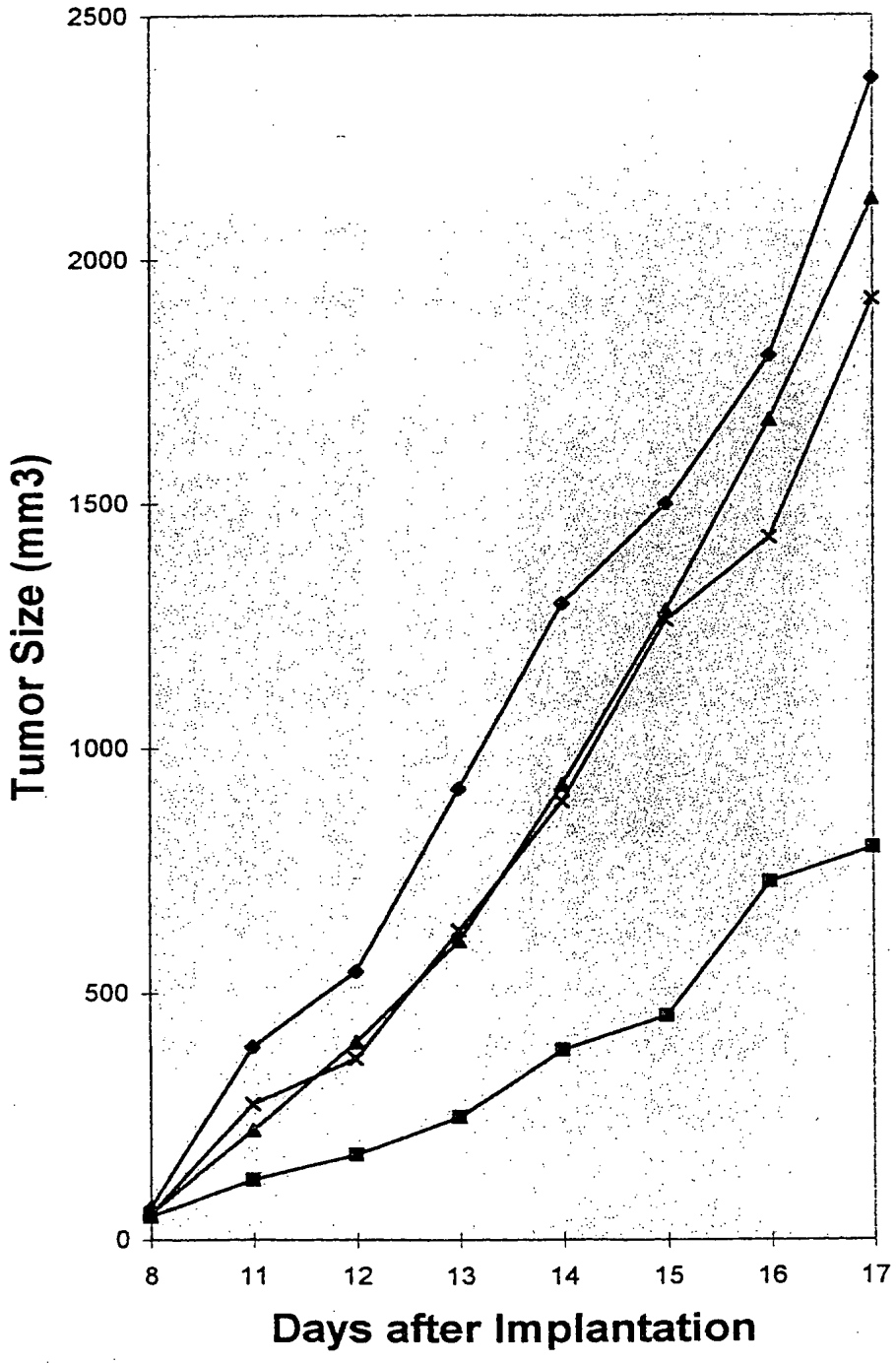
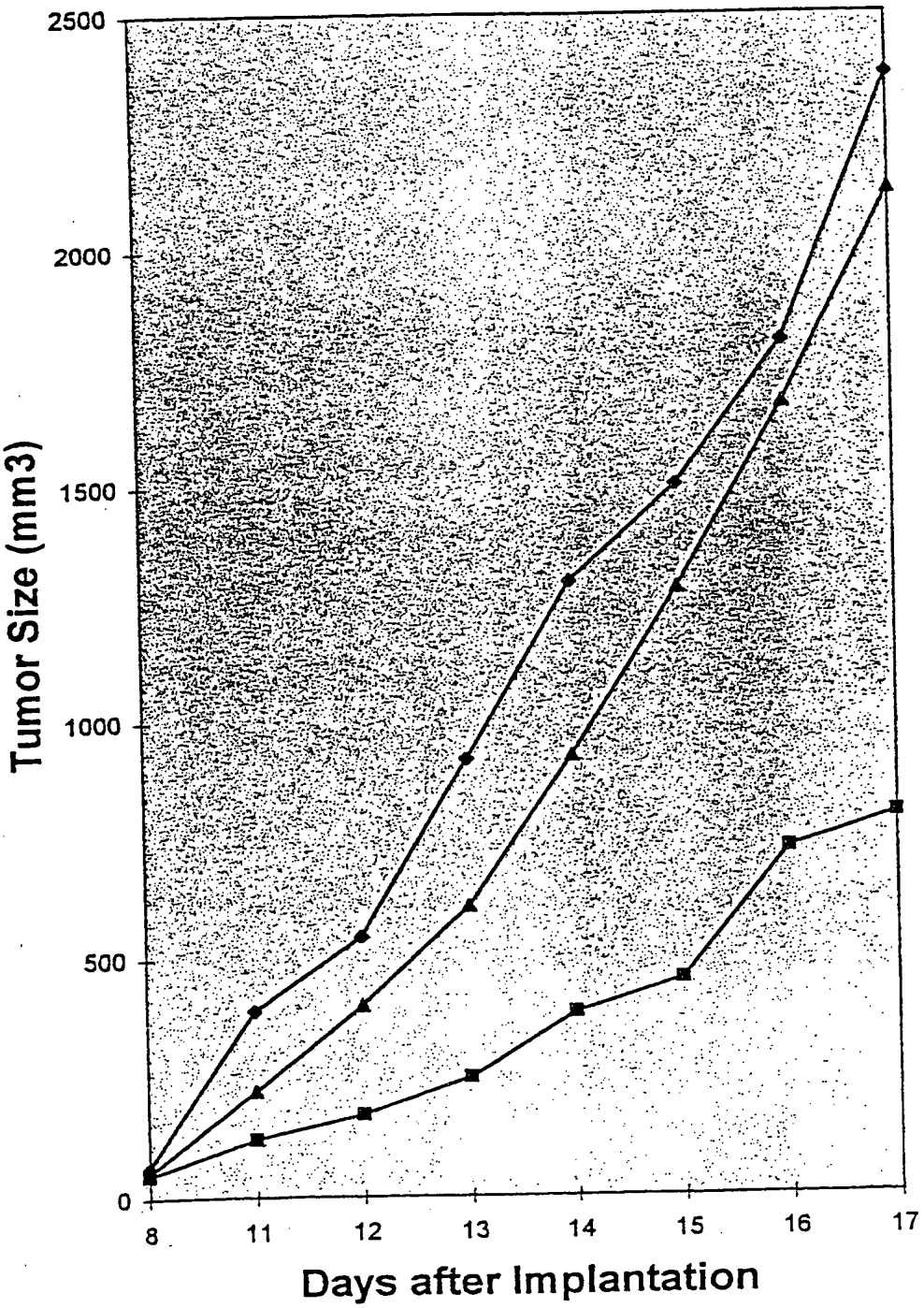


Fig. 43(B)



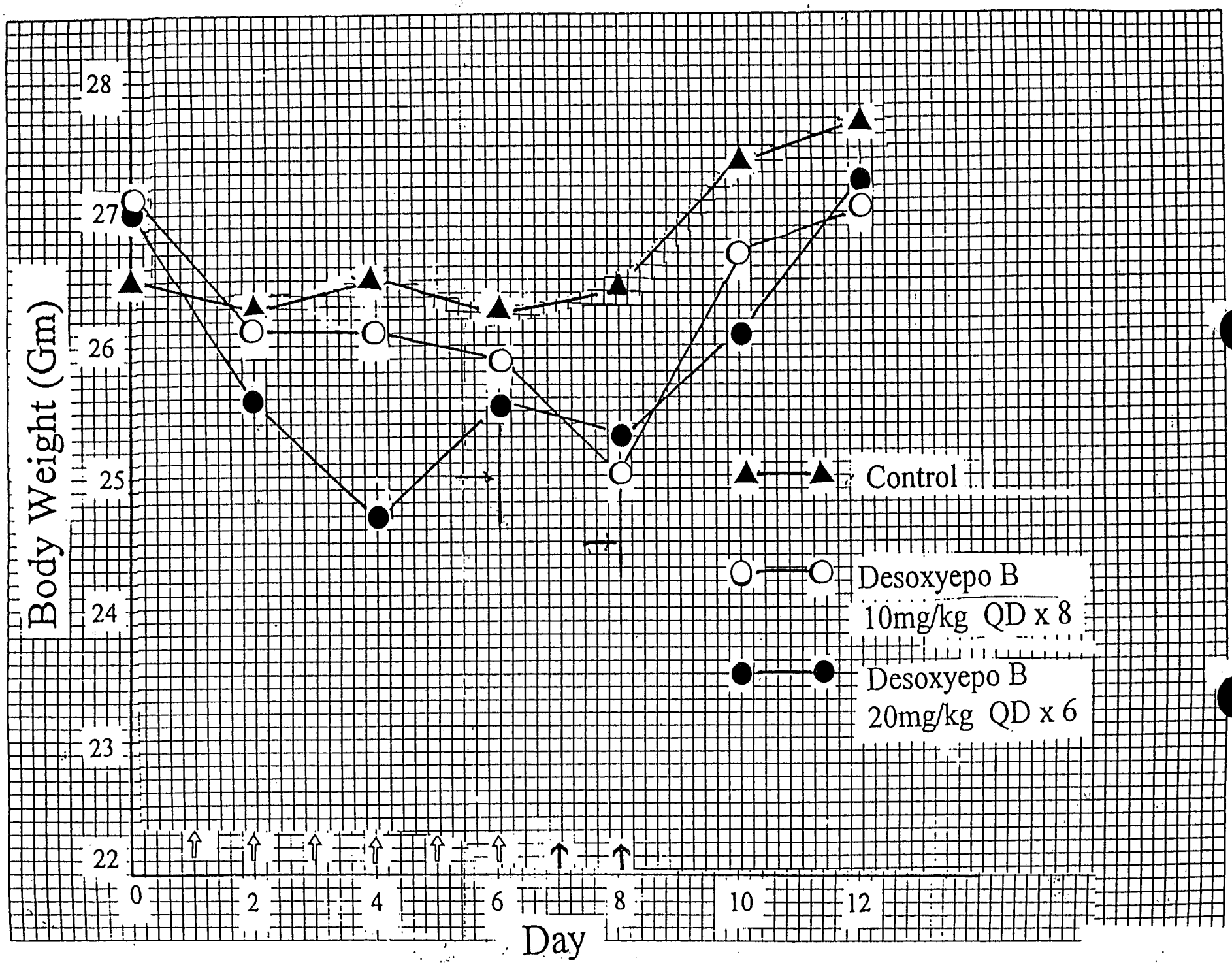

Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
Day
Control
Desoxyepo B
10mg/kg QD x 8
Desoxyepo B
20mg/kg QD x 6

Fig. 44(A)

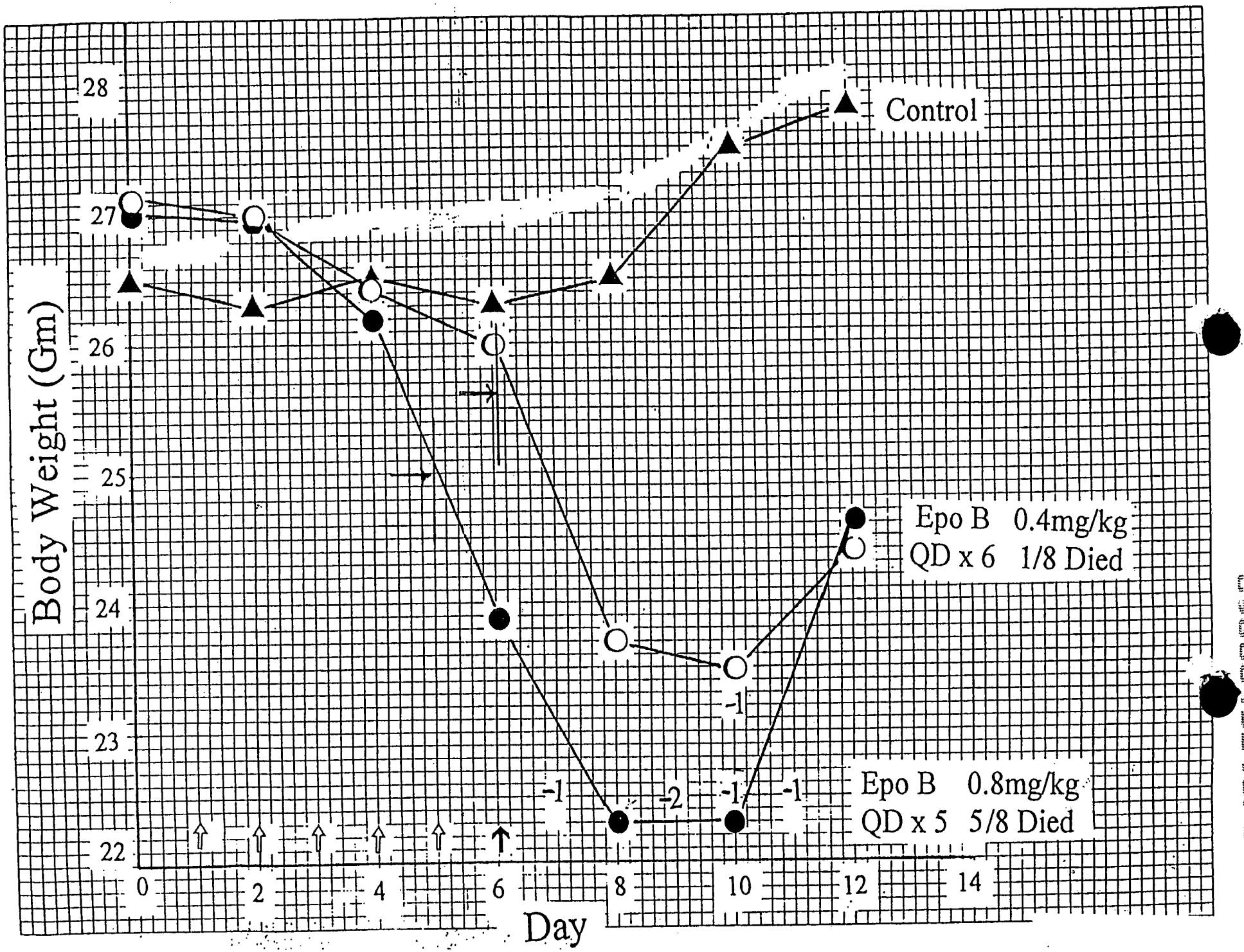

Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
14
Day
Control
Epo B 0.4mg/kg
QD x 6 1/8 Died
Epo B 0.8mg/kg
QD x 5 5/8 Died
-1
-1
-2
-1
-1

Fig. 44(B)

Fig. 45(A)

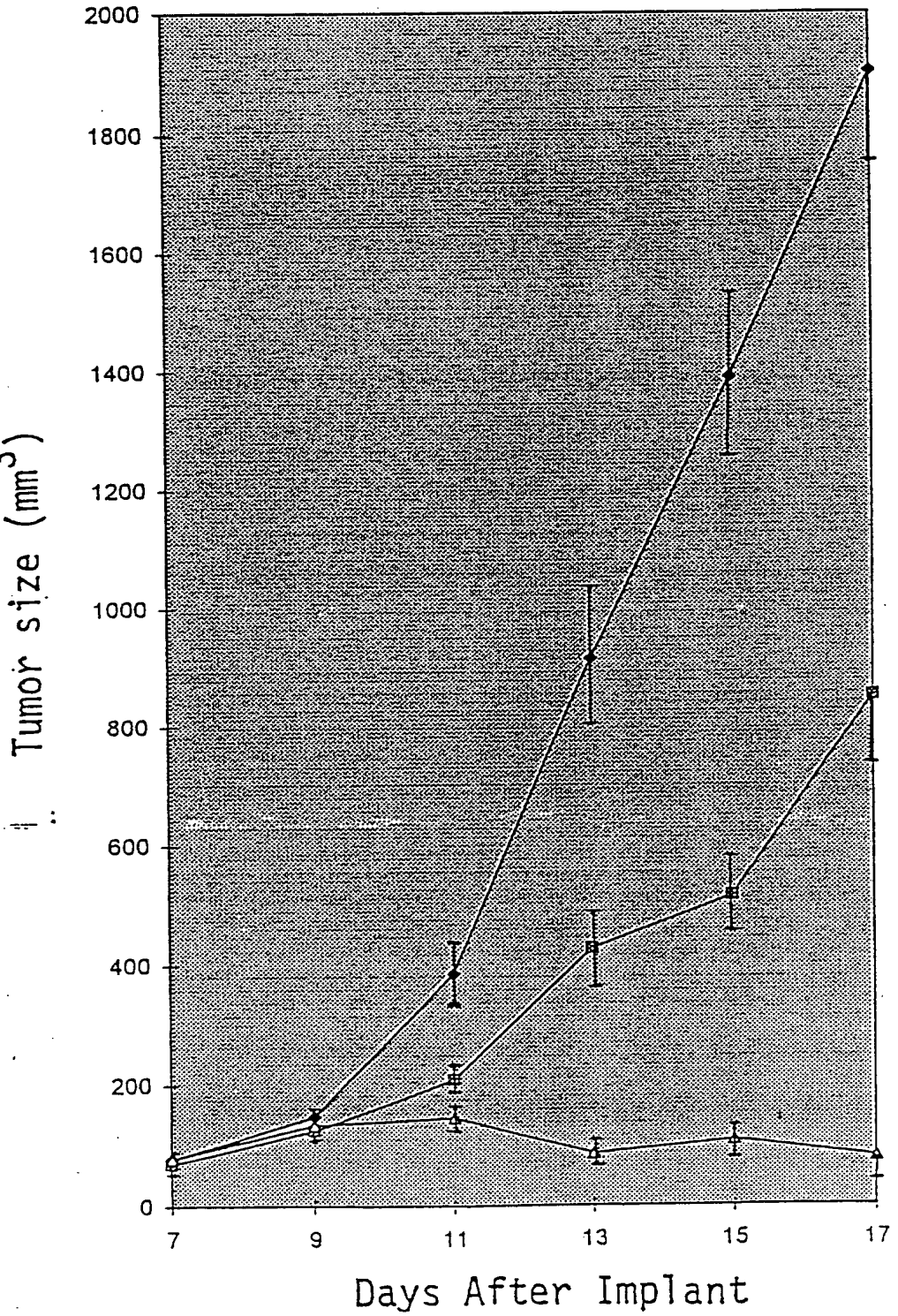
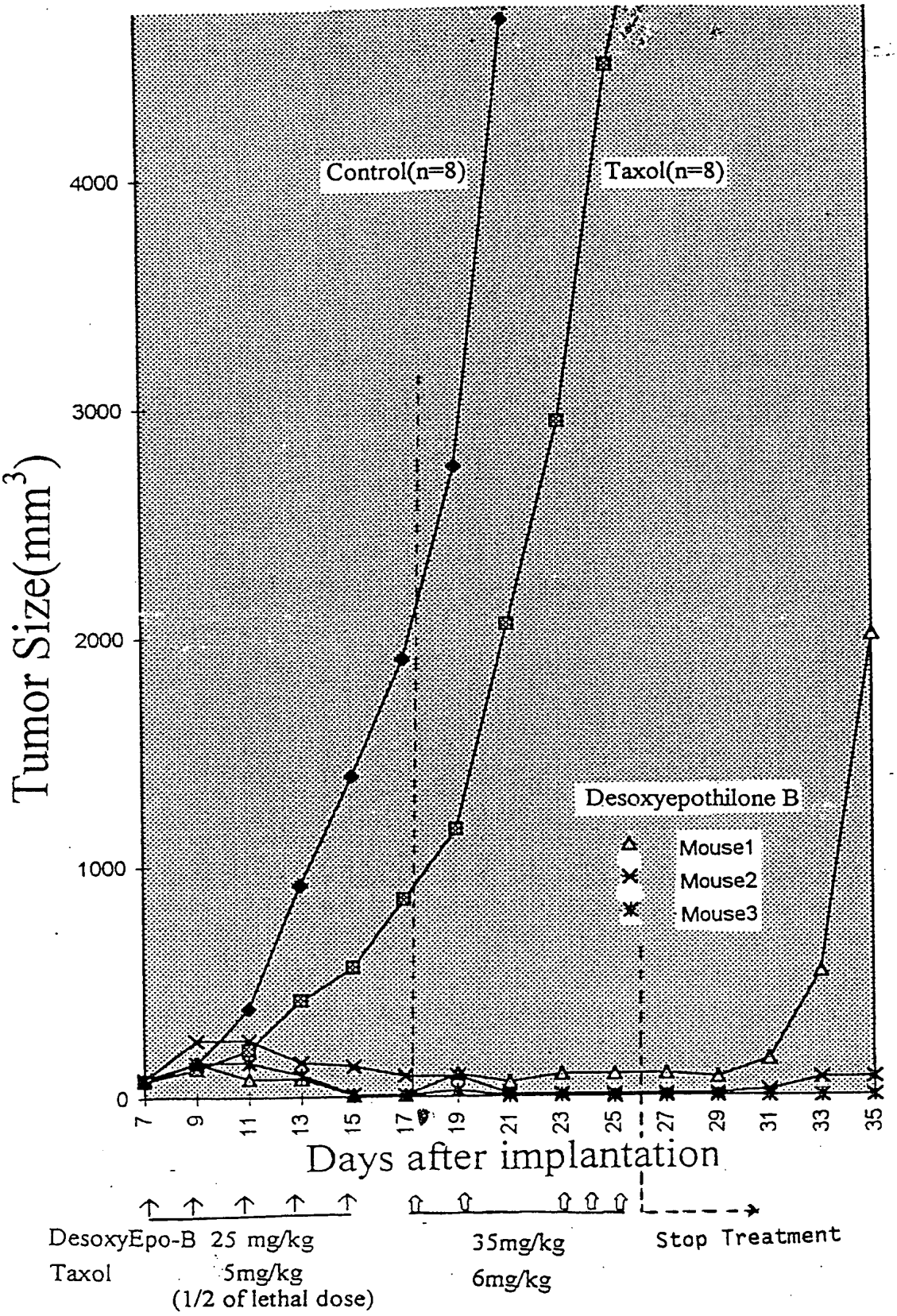


Fig. 45(B)



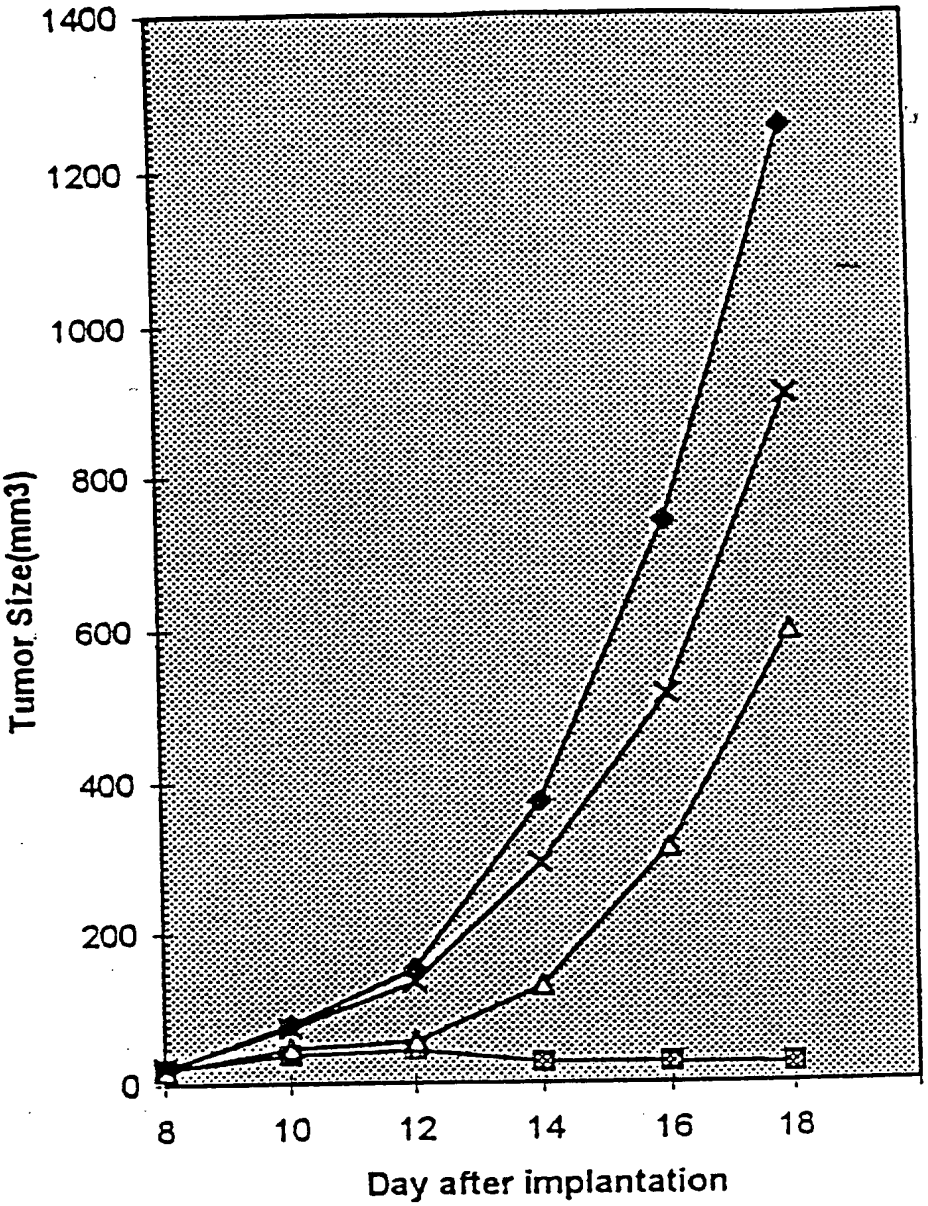
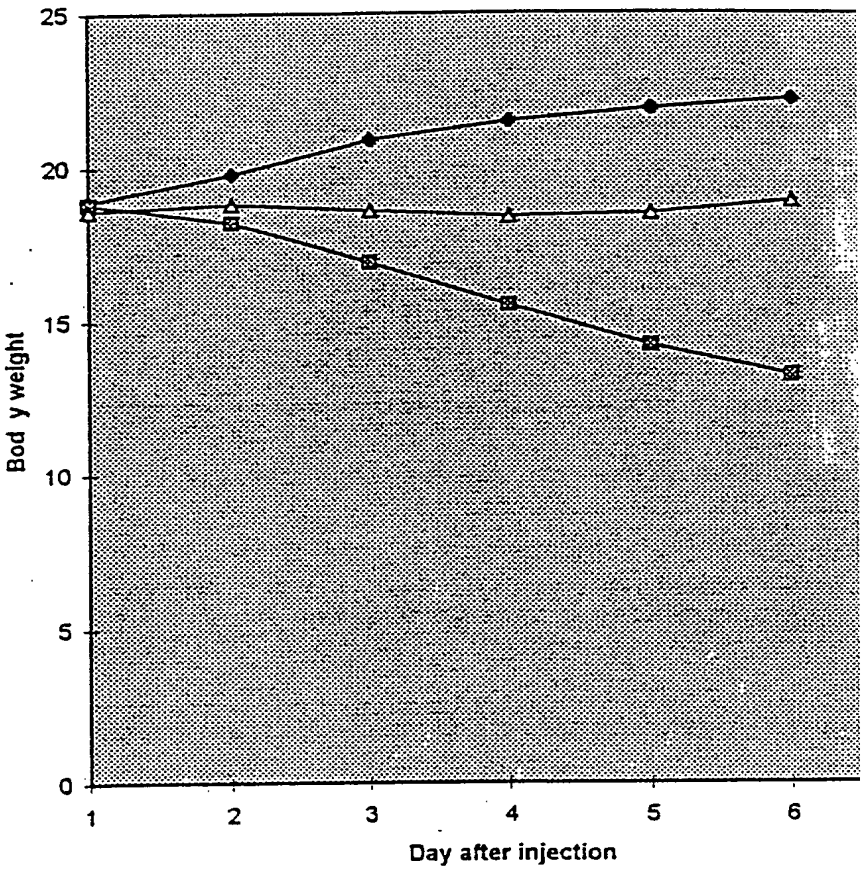
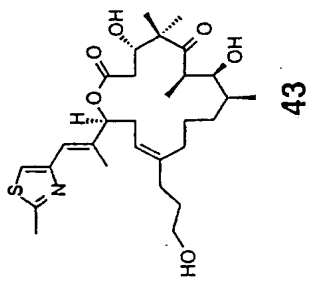

1400
1200
1000
800
600
400
200
0
Tumor Size(mm3)
8
10
12
14
16
18
Day after implantation

Fig. 46

Fig. 47





43

400 MHz, cdcl3, rt.

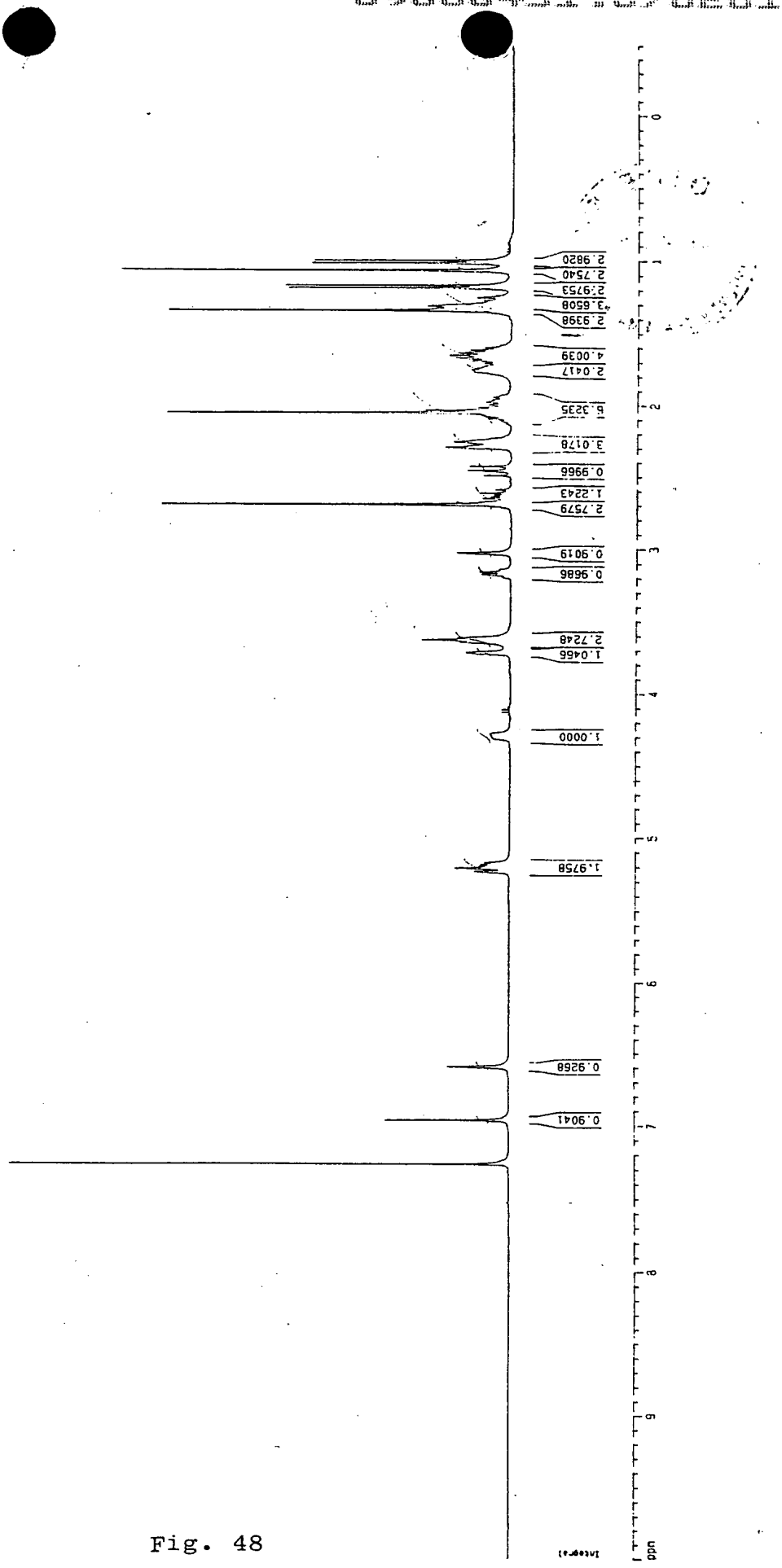


Fig. 48

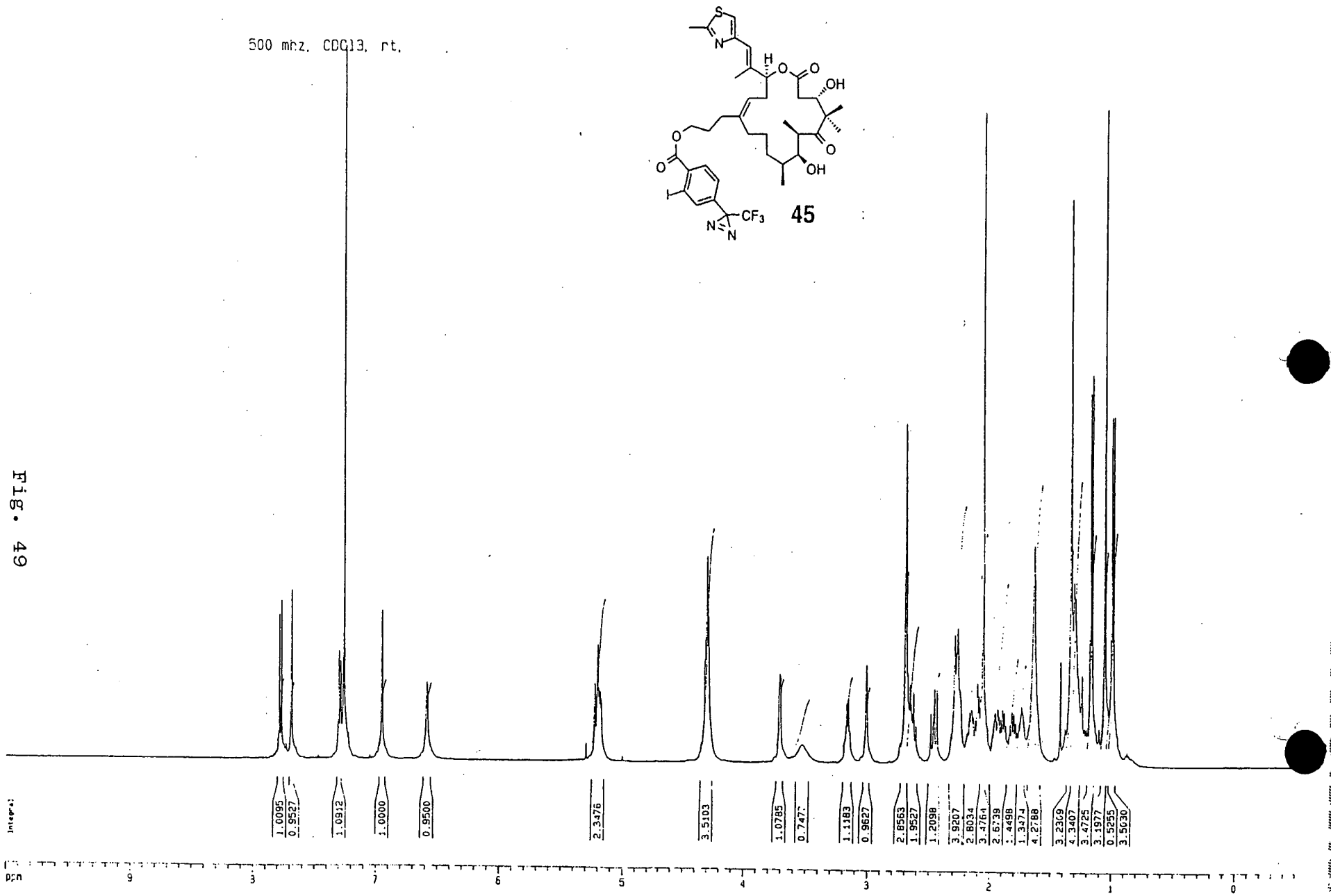
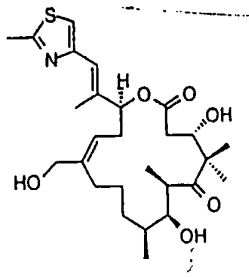
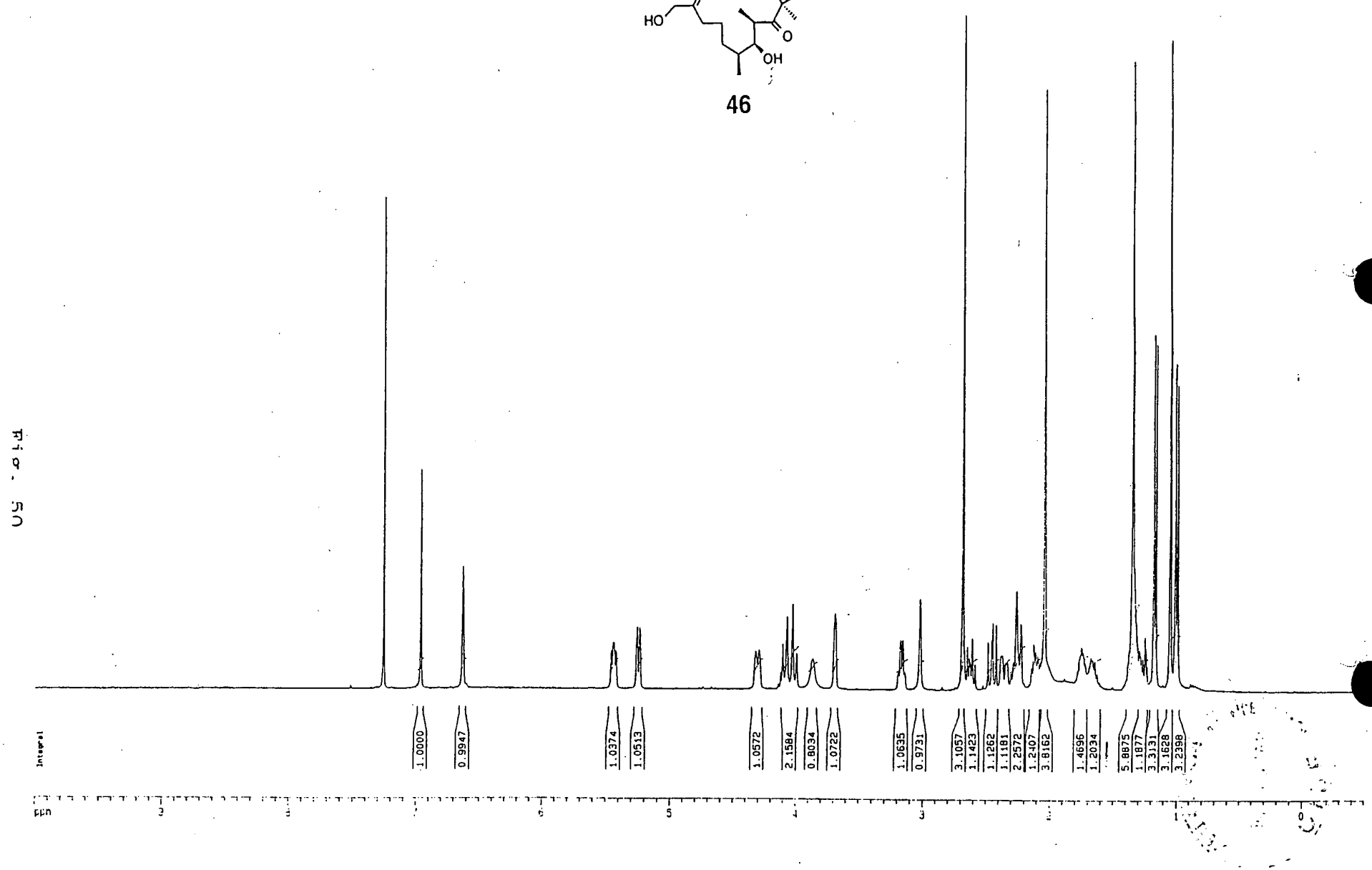

500 mhz, CDCl3, rt.
45
1.0095
0.9527
1.0812
1.0000
0.9500
2.3476
3.5103
1.0785
0.7477
1.1183
0.9627
2.8563
1.9527
1.2098
3.9207
2.8034
3.4764
2.6739
1.4498
1.3474
4.2788
3.2369
4.3407
3.4725
3.1977
0.5255
3.5030

Fig. 49

400 MHz, cdcl3, rt.



46



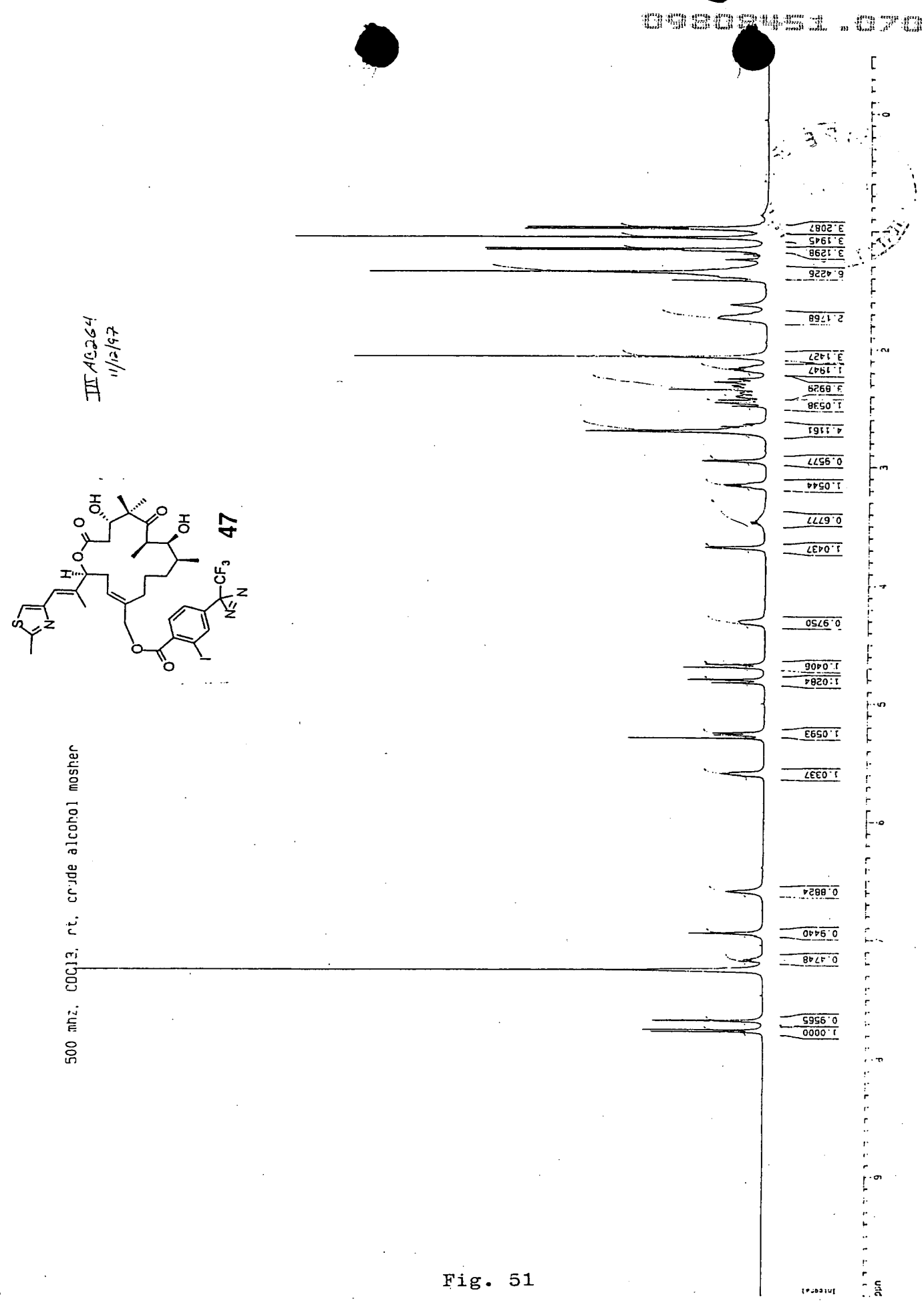

500 mhz, CDCl3, rt, crude alcohol mosher
III A9264
11/12/97
47
3.2087
3.1945
3.1298
6.4225
2.1768
3.1427
1.1947
3.0829
1.0538
4.1161
0.9577
1.0544
0.6777
1.0437
0.9750
1.0406
1.0284
1.0593
1.0337
0.8824
0.9440
0.7478
0.9565
1.0000

Fig. 51

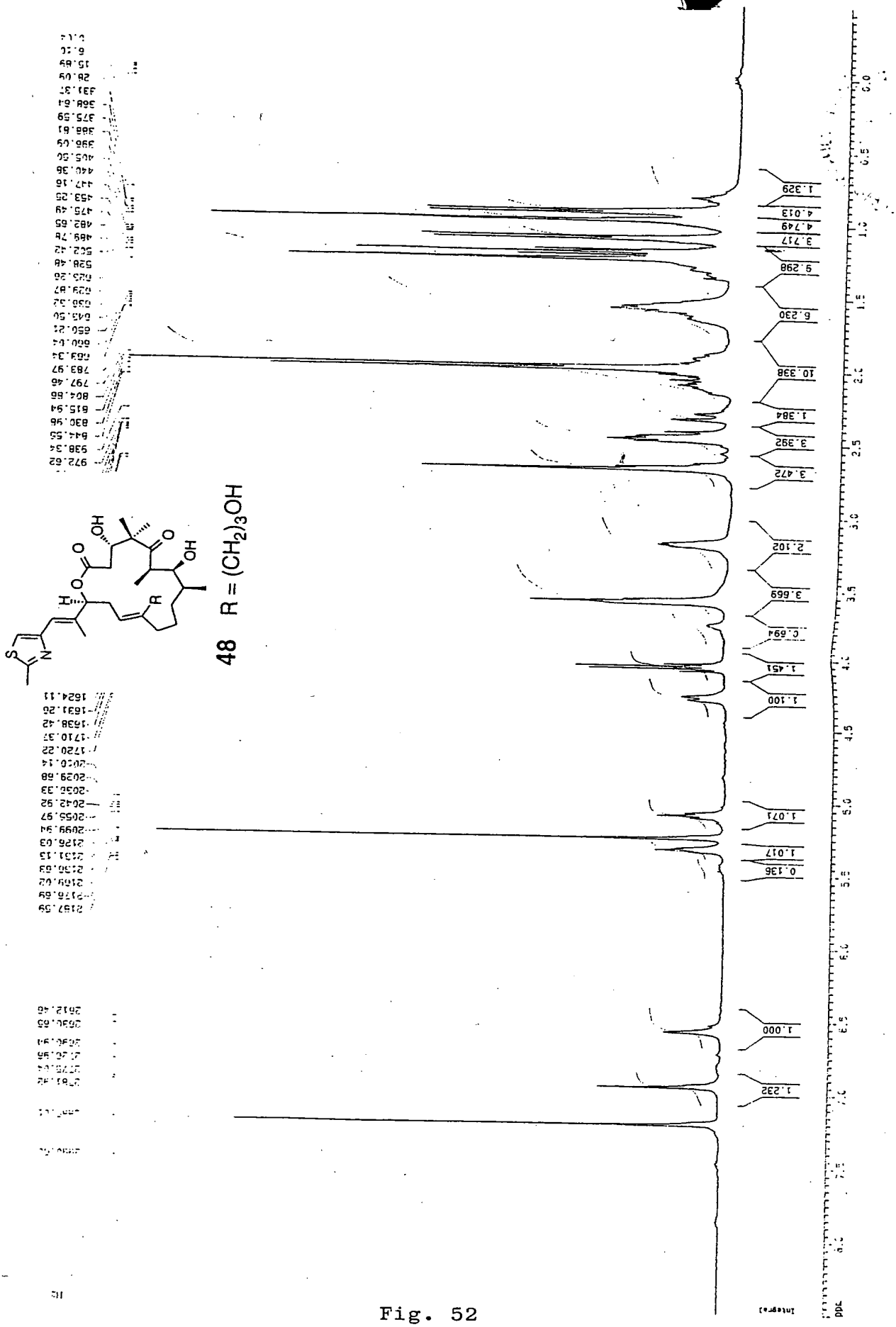


Fig. 52